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ISLET-CELL TUMOR OF THE PANCREAS WITH HYPERINSULINISM*

A Report of Six Cases

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ALTHOUGH in recent years many publications regarding patients with pancreatic islet-cell tumors have appeared, the condition is sufficiently infrequent to make additional reports desirable.[1] Since 1938 we have observed 6 patients in whom the diagnosis was verified at operation performed by one of us (L. S. McK.). Our experience with these patients forms the basis for the present paper. A report is particularly worth while at the present time because it provides a four-year to seven-year postoperative follow-up study of the patients concerned. In 5 of the 6 cases removal of a single adenoma at operation resulted in relief of symptoms that has persisted to date. In 1 case death followed seven weeks after operation, which disclosed an islet-cell carcinoma with multiple metastases in the liver. A summary of the data in these cases is given in Table 1.

CASE REPORTS

CASE 1.§ P. F., a 16-year-old girl was first seen on November 28, 1938. She had been well until the summer of 1933, when she began to have occasional spells of stupor that progressed into definite unconsciousness. In July of that year she was seen in the outpatient department of a children's hospital and in the next month at another hospital, where, while waiting for an examination after having missed the noonday meal, she fainted, remaining unconscious for about an hour; during this period she had a few convulsive twitchings of the shoulders and face and voided involuntarily. She was admitted for observation to the hospital, where she remained from August 18 to September 14. The fasting blood-sugar concentration was consistently low (of twelve determinations, ten were below 60 mg. per 100 cc., including five that were below 50 mg.). An attack of coma brought on by starvation was relieved by the intravenous injection of glucose; consequently, the diagnosis of hyperinsulinism was made, and the patient discharged with instructions regarding diet. She was readmitted on January 8, 1934, because in the week before entry attacks had occurred far more frequently than previously. During this admission, after extensive studies, abdominal exploration was carried out. No tumor was found; a small section of the tail of the pancreas removed for histologic examination was found to consist of normal tissue. The postoperative course was uneventful, and the patient was discharged on February 27 with instructions to follow a diet restricted in carbohydrate. The patient was subsequently seen in the Out-Patient Department on only one occasion, on March 16, 1934, when she reported that she had had no attacks since discharge from the hospital.

The patient was free from obvious attacks until August, 1938, when she suffered a recurrence of spells of drowsiness and weakness, particularly after an overnight fast. These symptoms were relieved by food or glucose. The attacks increased in frequency, and on November 8 she was taken to a third hospital in a deep stupor. On admission the blood-sugar concentration was 38 mg. per 100 cc. The patient was revived from her stuporous condition by means of concentrated glucose intravenously and sweetened orange juice orally. During a stay of 16 days in the hospital she was kept from hypoglycemia by frequent feedings. Roentgenograms of the chest, skull and abdomen gave normal findings; films of the teeth showed evidence of considerable infection. Electroencephalograms were thought to suggest that the patient, in addition to the overactivity of the sugar-disposing mechanism, had an epileptoid condition of cerebral dysrhythmia.

The patient was admitted to the New England Deaconess Hospital for further study on January 3, 1939. In the preceding days occasional attacks of hypoglycemia had continued. She had taken a bedtime lunch routinely, as well as orange juice at 3:00 o'clock each morning. Physical examination showed a small, thin, underdeveloped girl who seemed pale and listless. The body weight was 107 pounds (48.6 kg.) and the height 4 feet, 9½ inches (147 cm.). The teeth were poor; there was marked caries despite the extraction of 3 teeth a few days previously. The heart was normal in size and regular in rhythm, and over the whole precordium a prominent systolic murmur was audible. The abdomen was normal; there was a long healed operative scar in the left upper abdomen. The blood pressure was 104/70.

Questioning revealed that there had been no significant illnesses before 1933 and no abnormality except that discussed above. The father, mother, a brother and two sisters were living and well.

After 8:00 o'clock on the morning following admission the patient became increasingly drowsy, so that by the time breakfast was served — 45 minutes later — she was unconscious. The blood-sugar concentration was 28 mg. per 100 cc. The administration of glucose intravenously brought about prompt relief. During the next 2 weeks the patient was kept on a diet that included from 199 to 315 gm. of carbohydrate daily. By means of feedings between meals she was kept from hypoglycemic attacks.

The results of the glucose-tolerance tests in this case — and in the other 5 cases of the series — are shown in Table 2.

Examination of the urine showed no albumin, bile, diacetic acid or sugar, and examination of the sediment was nega-

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§A detailed account of the early history, studies and findings at the first operation in this case was presented by Boone[2] in 1934.

tive. Examination of the blood revealed a red-cell count of 4,660,000, with a hemoglobin of 82 per cent (Sahli), and a white-cell count of 10,150; the blood smear was essentially normal. The blood Hinton reaction was negative. The cholesterol content of the blood plasma was 163 mg. per 100 cc. The bromsulfalein test of liver function gave normal results. Roentgenograms of the skull and chest and of the region of the kidneys, ureters and bladder were normal. A gastrointestinal series was likewise normal; there was no change in the size and shape of the duodenal loop.

In view of the exacerbation of hypoglycemic attacks, it was thought justifiable to carry out a second pancreatic exploration despite the negative findings 5 years previously. Consequently, on January 16, exploration was performed under ether anesthesia through a long, curved transverse incision just above the umbilicus through both rectus muscles of the type used by Whipple.[3] Because of adhesions that had obliterated the lesser peritoneal cavity, painstaking dissection was necessary to free the stomach from the pancreas. The entire anterior aspect of the pancreas was exposed, from the extreme tip of the tail to the portion of the head that was visible anteriorly; the body and tail were then completely freed posteriorly. Inspection and careful palpation revealed no tumor in the part of the pancreas thus exposed. Attention was next directed to the remainder of the head of the pancreas. The entire head, together with the loop of duodenum, was elevated as much as the important vascular structures permitted. With the thumb and fingers of the examiner grasping the head of the pancreas, it was possible to feel a small tumor completely within pancreatic tissue. An exploratory incision brought into view a somewhat lobulated, encapsulated, reddish-purple nodule, which was completely removed; the rest of the organ was again palpated for other tumors, none being found.

The following was the description of the nodule by the pathologist:

> The tumor was a delicately encapsulated, reddish-brown, moderately yielding nodule, almost spherical, measuring 1.2 by 1.1 by 0.9 cm. On cross section it was found to be soft, moist, pale and reddish brown, with a few fine, gray foci indefinitely marked. Microscopic examination showed adenomatous tissue made up of beta cells.

The postoperative course was uneventful. Blood-sugar values during the first 48 hours ranged from 120 to 310 mg. per 100 cc., but during most of this time the patient was receiving glucose solution intravenously. From the 2nd postoperative day on, all random blood-sugar values were uniformly normal. Electroencephalograms taken after operation were normal. The patient was discharged from the hospital on February 4, in good condition.

On assays for insulin content the tissue was found to contain approximately 7 units of insulin per gram, or about twice the amount present in normal pancreatic tissue.*

After operation the patient continued in good condition. There were no attacks suggesting hypoglycemia, random blood-sugar values were normal and glucose-tolerance tests showed a normal response. The blood-sugar concentration on May 18, 1946, after an overnight fast, was 84 mg. per 100 cc. When last heard from in August, 1946, over 7 years after operation, the patient had continued to feel well.

CASE 2. L. H., a 49-year-old woman, was first seen on June 20, 1939. She had been well until January, 1931, when she began experiencing attacks of extreme weakness and drowsiness. During such periods she was unable to speak, felt listless and complained that the hands were cold and numb.

Examination revealed no satisfactory cause of the difficulty, but the patient seemed to improve on a high-carbohydrate diet, with frequent feedings; during spells of weakness she obtained relief by drinking orange juice. With the added food she gained in weight from 165 pounds in 1931 to 214 pounds in 1934. In May, 1934, the spells became severer. The patient was admitted to a hospital, where blood-sugar values as low as 42 mg. per 100 cc. were found. A glucose-tolerance test carried out for 4 hours was reported to be entirely normal. She progressed fairly well until November, 1938, when she was readmitted to the hospital with the same complaints. The weight at that time was 220 pounds, and the patient stated that for the preceding 4 years she had had one or two attacks a week, which were relieved by orange juice. A glucose-tolerance test carried out on November 21 showed the blood-sugar concentration after fasting to be 59 mg. per 100 cc.; following the administration of 170 gm. of glucose the value after the 1st hour was 183 mg., after the 2nd hour 155 mg. and after the 3rd hour 133 mg. per 100 cc. During the hospital stay in November the amount of carbohydrate in the diet was varied from 60 to 225 gm. daily, with no significant change in the condition except a loss in weight to 187 pounds.

The patient was admitted to the New England Deaconess Hospital on June 20, 1939. Physical examination showed an obese woman; the body weight was 186 pounds (84.5 kg.) and the height 63 inches (161 cm.). The heart was normal in size and regular in rhythm, and a moderately loud systolic murmur could be heard over the precordium. The lungs were clear, the abdomen normal, and the blood pressure 144/82. Examination of the blood revealed a red-cell count of 4,740,000, with a hemoglobin of 77 per cent (Sahli), and a white-cell count of 14,000, with a normal blood smear except for slight acromia. Examination of the urine showed 10 mg. of albumin per 100 cc., no sugar, diacetic acid or bile and a normal sediment. The bromsulfalein test of liver function gave normal results, and the blood bilirubin was 0.2 mg. per 100 cc. The basal metabolic rate was −10 per cent. A blood Hinton test was negative.

The past history was essentially noncontributory. The family history was irrelevant; the patient had three grown children — one son and two daughters — living and well.

During the first 9 days in the hospital the patient appeared generally dazed, with slow reactions. Blood-sugar values as low as 31 mg. per 100 cc. were found. Roentgenograms of the skull were normal, as was a gastrointestinal series, in which the duodenal sweep seemed of normal extent.

Exploratory laparotomy was carried out on June 28, under ether anesthesia, through a transverse incision. The pancreas was easily exposed and freed from its attachment without difficulty, disclosing a small nodule at about the midportion of the organ on the anterior aspect near the lower border. Incision showed it to be a soft, friable, purplish tumor that on section was found to include considerable grayish necrotic material. The tumor was well encapsulated and could be completely removed, although because of its friability, during the removal it broke into two parts, the larger of which was 8 mm. in diameter. Careful inspection and palpation failed to disclose any other tumors. Microscopic examination showed the nodule removed to be an islet-cell adenoma made up chiefly of beta cells. Assay showed the tumor to contain more than 100 units of insulin per gram.

The postoperative course was uneventful, and the patient left the hospital in good condition on July 20. Except for fasting blood-sugar values of 130 mg. and 120 mg. per 100 cc., for the 1st and 2nd days respectively after operation, all values postoperatively were normal and the patient was entirely free from hypoglycemic attacks. A glucose-tolerance test carried out on July 18 gave entirely normal results (Table 2).

The patient reported for examination on October 18, 1939, May 21, 1940, and May 29, 1942, when questioning revealed no symptoms suggesting hypoglycemia and careful study, including glucose-tolerance tests, yielded results within normal limits except that, in general, blood-sugar values 4, 5 and 6 hours after the administration of glucose tended to be subnormal or toward the lower limit of normal. The patient remained entirely asymptomatic, however, and blood-sugar values after an overnight fast were normal. In the last letter received from her, dated August 4, 1946, she stated that she had been well and active.

CASE 3.† F. P. H., a 58-year-old woman when first seen on September 15, 1938, had been well until June, 1935, when she had had an attack of fainting followed subsequently by periods of coma during which she slept 12 to 48 hours. At times she suffered blankness of vision. In 1936, adopting a suggestion from a newspaper article, she began to take sugar for the attacks and found that this gave relief. The periods of drowsiness, mental confusion and speech disturbance continued, however. The patient first consulted a physician in October, 1937, when fainting spells were occurring once or twice daily and often on awakening at about 5:00 a.m. She entered a hospital on June 23, 1938. The fasting blood sugar,

*All assays in these cases were performed by Mr. George B. Walden, of the Research Laboratories of Eli Lilly and Company, Indianapolis, to whom frozen portions of the tumors were sent.

†Previously reported in part by Gray.[4]

which was 27 mg. per 100 cc. 2 days later, was subsequently found to average about 45 mg. The patient was put on a low-carbohydrate, low-protein, high-fat diet, on which she did fairly well for a time, but returned later because of recurrence of symptoms and the need of increasing the feedings to every 2 or 3 hours to prevent attacks. A diagnosis of probable islet-cell tumor was made.

During the first admission to the New England Deaconess Hospital in September, 1938, studies confirmed this diagnosis. Fasting blood-sugar values as low as 30 mg. per 100 cc. were obtained, and on one occasion, after exercise, a value of 20 mg. was reported. Roentgenograms of the heart, lungs, skull and gastrointestinal tract were normal. Examination of the ocular fundi gave normal findings. The basal metabolic rate was −7 per cent. The blood calcium was 10.1 mg., and the blood phosphorus 3.8 mg. per 100 cc. The bromsulfalein test of liver function gave normal results. An electrocardiogram was essentially normal. The blood Hinton reaction was negative.

The past and family histories were irrelevant. Review of systems revealed nothing of consequence except for "nervousness" and for exertional dyspnea noted since a gain in weight.

Physical examination showed an obese, healthy-appearing woman. The body weight was 188 pounds (85.5 kg.), and the height was 63 inches (161 cm.). Examination of the heart, lungs and abdomen was essentially negative, and the blood pressure varied from 115/65 to 160/80.

Abdominal exploration was advised but was refused by the patient. Although she promised to return soon for operation, actually she did not re-enter the hospital until September 12, 1939. Within a month or so following discharge in 1938, she had fallen at home, suffering injuries that kept her in bed for 28 weeks. The hypoglycemic attacks had continued during the year and had been particularly frequent and marked after resumption of physical activity. Unless food was taken about every 3 hours, vision became blurred and mental dullness, stupor, unconsciousness and, at times, convulsions followed. During the 2 weeks prior to the second admission a special nurse had been in attendance in the home and had awakened the patient every 2½ hours for feedings during the night.

Physical examination showed the patient to be even more obese than at the former visit — 203 pounds (92.3 kg.), as compared with 188 pounds (85.5 kg.) a year previously. The heart seemed normal in size and was regular in rhythm; a slight generalized systolic murmur could be heard. The lungs were clear, and the abdomen normal to palpation. The fasting blood sugar on the morning after admission was 29 mg. per 100 cc. Examination of the blood showed a red-cell count of 4,540,000, with a hemoglobin of 86 per cent (Sahli), and a white-cell count of 12,700, with a normal differential. The urine contained a trace of sugar but no albumin, bile or diacetic acid, and the sediment was essentially normal. The blood nonprotein nitrogen was 31 mg., and the cholesterol content of the blood plasma 153 mg. per 100 cc. (the free cholesterol was 35 mg. per 100 cc.).

It was soon evident that unusual precautions were essential to keep the patient from becoming hypoglycemic. The blood-sugar values were so low and the attacks were so frequent, despite careful supervision, that early exploratory operation was carried out 4 days after admission. A transverse incision was made, and the pancreas exposed through the gastrocolic omentum. After mobilization of the organ a tumor about 1.5 to 2.0 cm. in diameter was visible toward the tip. This region of the pancreas, which was adherent to adjacent structures, lay high and was accessible only with great difficulty. Finally it was freed, and resection of the tip of the organ was carried out, although not more than 3.0 to 3.5 cm. of the pancreas was removed. The tumor was firm and seemed to infiltrate surrounding tissue, suggesting a malignant process. The liver was studded with grayish-white nodules varying in diameter from several millimeters to about 2 cm. A wedge from one of these nodules was excised and examined.

The postoperative course was extraordinary. For the 1st week blood-sugar values were within normal limits. Then on September 23, a week after operation, small amounts of sugar appeared in the urine, and a capillary blood-sugar value at 11:00 a.m. was 200 mg. per 100 cc. In the next 3 days glycosuria and glycemia increased, so that urine tests for sugar by the Benedict method ranged from yellow to red, and the fasting blood sugar on September 27 was 247 mg. per 100 cc. Consequently, treatment with protamine-zinc insulin was instituted and continued for a total of 29 days in a dosage of 12 to 16 units daily before breakfast. The food intake during this period was variable because of the patient's condition; the amount of carbohydrate taken daily averaged 149 gm., that of protein 41 gm. and that of fat 35 gm. On this regime, fasting blood-sugar values varied from 120 to 150 mg. per 100 cc. From October 25 until the patient's death on November 3 no insulin was used.

In the few days immediately following operation, the patient's general condition was much improved. Then, however, crepitant rales were heard at the lung bases, sibilant rales were heard throughout the chest, and moderate fever was present. Roentgenograms showed patches of bronchopneumonia in the lower half of both lung fields. From the day of operation, September 16, until September 19, the patient received a constant infusion of glucose into a vein at the elbow of the right arm. An area of induration and tenderness developed above the antecubital space on the outer aspect of the arm; the inflammation gradually subsided but healing never entirely took place, and on October 21 the right arm was more swollen than before. At that time generalized anasarca also developed. The right external jugular vein became palpable and tender. The clinical impression was that the swelling of the right arm did not represent an infection, but rather edema secondary to venous thrombosis. Later, however, a hard, slightly tender area about 5 cm. in diameter developed in the right lower axilla; on October 10 this was incised, allowing 60 to 90 cc. of thick pus to drain.

Immediately after the abdominal operation the body temperature rose to a maximum of 103°F. and then ranged between 99 and 101°F. for 4 or 5 weeks before completely subsiding. The operative wound in the abdomen healed readily except for a portion on the left side, where a sinus persisted; during the 2nd, 3rd and 4th weeks after operation, large quantities of creamy, yellow pus drained from this wound. During that time, there were nausea and upper abdominal pain made worse by eating, so that for a considerable period the patient was maintained on glucose given subcutaneously. During the last 2 weeks of life the amount of drainage from the operative wound subsided.

Throughout the postoperative course and, indeed, before operation the breathing was rapid, somewhat labored and wheezing in type. By October 28, however, the patient seemed better in almost every way and the breathing was easier and quieter. On November 2 she was allowed up in a chair for a short period. On November 3, after she had been up about 30 minutes and was ready to return to bed, she developed an acute attack of shortness of breath and quickly became comatose, pulseless and cyanotic. She rapidly failed and died within a few minutes.

Autopsy. At post-mortem examination no evidence of residual tumor was found in the pancreas. The liver was studded with many firm, white, glistening, well demarcated nodules varying from 2 to 3 cm. in diameter. The tumor replaced one third to half the liver substance. Histologic examination of the tumor tissue previously removed from the pancreas and liver at operation, and of that obtained from the liver at autopsy, showed the growth to be an islet-cell carcinoma of mixed type. Beta cells were demonstrated in the primary tumor but not in the metastatic lesions. Microscopic examination of the pituitary gland revealed marked basophilism. In addition to these findings, autopsy disclosed extensive thrombophlebitis of the right brachial, right axillary, right subclavian and right internal jugular veins, with complete occlusion of these vessels. There was thrombosis of the superior vena cava, with partial organization and occlusion. The immediate cause of death was pulmonary embolism; there were emboli in most of the secondary ramifications of the pulmonary artery. There were recent and old infarcts to the lower lobe of the right lung. (Detailed autopsy findings in this case, together with photomicrographs, appear in the article by Gray.[4])

Attempts in the laboratory of the New England Deaconess Hospital to determine the insulin content both of the primary tumor and of the nodules were unsuccessful from a quantitative standpoint, probably because of unfamiliarity with the technic. A moderate lowering of the blood sugar was obtained, however, in a rabbit following the injection of an extract of liver nodules.

CASE 4.* B. M., a 29-year-old housewife, was seen in the Out Patient Department of the Massachusetts General Hospital on August 14, 1940, and was admitted as an inpatient on September 12. She had been well up until December, 1937, when she began to experience attacks of weakness, dizziness, faintness and sweating and a feeling as if her mind were "paralyzed." At 11:00 a.m. on December 24, while at work at her sewing machine, she began to perspire profusely, her mind became blank and she fainted; unconsciousness lasted 17 hours. After this episode she gave up her job and remained at home for 5 months. She then resumed work, but after 4 or 5 weeks had another fainting spell while at work; on this occasion she was unconscious for 18 hours. Following another attack 2 days later, she was admitted to a hospital, where the blood sugar was found to be only 35 mg. per 100 cc. and roentgenograms of the skull were said to show no sign of tumor. She was placed on a special diet but found that to keep comfortable she always had to eat more than prescribed, and she had adopted a regime of eating between meals and at bedtime, in addition to the regular three meals. She had gained 40 pounds in weight in 2½ years. Although with such treatment she felt better and gained weight and strength and the attacks of syncope became milder, they seemed to occur almost as frequently as before (three or four times a month) — more frequently at the time of the menstrual period. The patient stated that during attacks she seemed unable to complete an action already started. The attacks were always relieved or aborted by food or glucose, and later the patient could recall nothing regarding the attack and chills and a "frozen feeling" were often present for some time.

A review of the past history showed no important illnesses; the patient remembered only measles and influenza in childhood. The family history was irrelevant except that two paternal aunts had died of cancer. The patient had been married for five years and had one child 3 years old.

Physical examination showed no significant abnormalities. The upper teeth were replaced by a satisfactory denture. The blood pressure was 118/85. The body weight was 124 pounds (56.5 kg.) and the height 61½ inches (156 cm.).

On August 14, 17 and 21 the fasting blood-sugar values were 38, 35 and 41 mg. per 100 cc., respectively, and on September 13, 14, 27 and 30, they were 26, 30, 25 and 40 mg., respectively. Examination of the blood revealed a red-cell count of 4,940,000, with a hemoglobin of 90 per cent, and a white-cell count of 10,500, with a normal differential. The urine contained no albumin, sugar, bile or diacetic acid, and the sediment was normal. A blood Wassermann test was negative. The serum chloride was 99.6 and 108.1 milliequiv. per liter on two occasions. The blood cholesterol was 144 mg., the serum nonprotein nitrogen 24 mg., and the serum protein 7.0 gm. per 100 cc. The basal metabolic rate was −6 per cent. Roentgenograms of the gastrointestinal tract, chest and skull were negative.

On October 7 exploratory laparotomy was carried out through a wide transverse incision under nitrous oxide, oxygen and ether anesthesia. Considerable difficulty was experienced in locating a tumor, and even more trouble in removing it. It was finally found in and removed from the substance of the head of the pancreas; after removal, the tumor was found to have been directly over the beginning of the portal vein, which was not damaged during the operation. The tumor was definitely encapsulated and was soft, friable and purplish. During removal it was broken up into small fragments; the total weight was 750 mg. Assay showed a normal insulin content (3 units per gram). Histologically the tumor was an islet-cell adenoma.

The postoperative course was uneventful. The fasting blood sugar, which on the morning of October 8 was 155 mg. per 100 cc., was 127 mg. on October 9 and 93 mg. on October 11. Following this the blood sugar stabilized at an entirely normal level and continued so until discharge on October 28.

The patient was seen in the Out Patient Department of the Massachusetts General Hospital on December 20, about 2½ months after operation. She had had no spells of weakness or fainting, although the appetite continued to be extraordinarily good. At this visit a blood-sugar determination about 12 hours after a meal was 67 mg. per 100 cc.; another determination, made 2 hours later and still in the fasting state, was 76 mg. per 100 cc. At a visit on July 2, 1941, the blood sugar 4 hours after eating a sandwich and milk was 97 mg. per 100 cc. The patient had continued to feel entirely well and weighed 118 pounds. She was last seen on January 8, 1944, when the fasting blood sugar was 102 mg. per 100 cc. In a letter dated April 26, 1946, she stated that she was doing all the housework for her family of five and that her appetite, weight and energy were normal.

CASE 5. E. R., a 32-year-old bartender and taxi driver, had been admitted to a hospital on October 1, 1940, with the complaint that for a year he had experienced attacks of twitching of the face and neck, staggering in gait, weakness, dizziness and sleepiness, all relieved by food. Blood-sugar studies had shown extremely low values, and the diagnosis of probable islet-cell tumor was made. At operation on October 15 no tumor could be felt in the pancreas. The blood-sugar values continued to be low, and attacks persisted despite a high-protein, low-carbohydrate diet and phenobarbital daily.

Questioning on admission to the New England Deaconess Hospital on October 23, 1941, revealed that the symptoms had included the following: drowsiness leading to unconsciousness, weakness, sweating, rapid heart action, trembling and nervousness, numbness especially about the lips, inability to concentrate or to think clearly, staggering gait as that of a drunken man, twitching of the hands and face, pugnaciousness, aggressiveness and blurring of vision. The first symptom usually noted was drowsiness. Attacks were definitely brought on more easily by exercise and by prolonged abstinence from food; food gave almost immediate relief. The patient first noticed his trouble because of difficulty at times in tying his tie. As a bartender he got along fairly well, because he could usually forestall attacks by taking food, but even so, at times he confused orders. Once while a taxi driver, he pulled his car up to the curb, got out and walked aimlessly for 5 blocks before a friend saw that something was wrong and took care of him; afterward, the patient did not recall the incident.

Physical examination showed no abnormalities. The patient seemed well developed and well nourished; the blood pressure was 104/70. The body weight was 166¾ pounds (75.8 kg.). Examination of the ocular fundi gave normal findings. Examination of the blood revealed a red-cell count of 5,070,000, with a hemoglobin of 17.7 gm. per 100 cc., and a white-cell count of 10,650, with a normal differential. The urine contained no albumin, sugar, bile or diacetic acid, and examination of the sediment was negative. The serum protein was 6.4 gm. and the nonprotein nitrogen 30 mg. per 100 cc., and the serum chloride 97.3 milliequiv. per liter. Roentgenograms of the skull, chest and gastrointestinal tract were negative. An electrocardiogram was normal.

At exploratory laparotomy on October 30 a completely encapsulated, soft tumor measuring 1.5 by 1.5 by 1.7 cm. was removed from the pancreas. The tumor was a mottled red-gray in color. On microscopic examination it proved to be an adenoma of insular origin, consisting chiefly of beta cells, with scattered foci of ductal epithelium. Under sterile conditions Dr. J. Herbert Waite transplanted a small section of the tumor into the anterior chamber of the eye of a normal rabbit; the tumor failed to develop, however, and no signs of excessive insulin activity were evident from periodic tests of the rabbit's blood sugar.

Following operation the patient developed bronchopneumonia at both lung bases, particularly the left. Consequently he was uncomfortable during the first several days after operation, but gradually improved and left the hospital on December 1 in good condition. From his home physician it was learned that as late as May, 1946, he had continued to feel well and had had no attacks suggesting hypoglycemia.

CASE 6. S. F., a 45-year-old farmer, was admitted to the New England Deaconess Hospital on November 8, 1941. He had felt well until 2 years previously, when he began to notice dizziness brought on particularly by exercise and relieved by eating. Symptoms gradually increased to include weakness, fatigue and at times a change in temperament, irritability and a feeling of mental confusion. Various types of medical treatment had proved ineffective. The first indication of difficulty had occurred in the spring of 1938 while the patient was plowing corn. He noticed increasing difficulty and finally, when he stopped and let go of the reins, which had been partly supporting him, he felt dizzy and sank to

*This case was reported in 1941.[5] Permission to include the patient in the present series was given by the Executive Committee of the Massachusetts General Hospital.

the ground. When he finally got to the house and obtained food, he felt relieved at once. This episode was the beginning of a long series of similar experiences. He soon adopted a schedule of taking orange juice or other food as soon as he arose in the morning, before starting work. During the last several months he had had to give up most of the work about the farm because of the danger of hypoglycemic attacks. He ate regularly between meals and carried sugar in his pocket at all times. When attempts were made to arouse him from a hypoglycemic stupor, he was occasionally simply confused and co-operated with difficulty; at other times he was pugnacious.

The family and past histories, except as already stated, were irrelevant.

Physical examination showed a well developed and well nourished man. The body weight was 208 pounds (94.5 kg.). The heart, lungs and abdomen were normal, and the blood pressure was 110/70.

Examination of the blood showed a red-cell count of 4,920,000, with a hemoglobin of 15 mg. per 100 cc., and a white-cell count of 9600, with a normal differential. The urine contained only a slight trace of albumin and no sugar, bile or diacetic acid; examination of the sediment was essentially negative. The blood sugar on November 10 was 41 mg. per 100 cc. Subsequent values were uniformly at a low level, usually below 50 mg. per 100 cc.

Operation was carried out on November 18 under nitrous oxide, oxygen and ether anesthesia. A long transverse incision was made across both rectus muscles. Exposure of the pancreas was quite difficult. The capsule was incised along the lower margin, and the pancreas lifted from its bed so that it could be carefully palpated between the fingers from the tip of the tail to the junction of the superior mesenteric and splenic veins. The free margin of the duodenum was then mobilized so that the head of the pancreas could be palpated between the fingers, the exploration being carried up to the point at which the pancreas had been explored from the other approach. Throughout this procedure nothing abnormal was seen or felt except that at the free margin of the head in the duodenal loop, there was a small, firm area about 1 cm. in diameter within the pancreatic tissue. Although this area did not seem unusual, in the absence of any other abnormality, it seemed necessary to explore it further. This proved difficult, because of the extreme vascularity of the region. By blunt dissection a deep, purplish, encapsulated tumor about 1 cm. in its greatest diameter was removed in one piece. Histologic examination showed an adenoma of the islet cells, with hyalinized stroma.

The postoperative course was uneventful. No further hypoglycemic attacks were experienced, and the blood-sugar values were within the normal range. The patient continued to be well. On August 4, 1946 (almost 5 years after operation), the patient stated in a letter that he had been in excellent health and had had no further difficulty of the sort experienced prior to the operation.

Discussion

The 6 cases reported above are instructive in that they illustrate the various problems encountered in the diagnosis and treatment of patients with hyperinsulinism. Of especial interest are the patients in Cases 1 and 5, in whom no tumor had been found at a previous operation elsewhere, and the patient in Case 3, who was found to have a malignant tumor with metastases in the liver.

Symptomatology

Although the symptoms experienced by the patients were those common to reactions due to an overdose of insulin, in general they lacked the acute nature encountered following unmodified insulin. Although these patients often experienced sweating and nervousness, the symptoms were usually increasing mental confusion, bizarre behavior and drowsiness that finally passed into total unconsciousness, with or without convulsions. Such symptoms developed if food was withheld for more than a few hours, and an overnight fast invariably resulted in a blood-sugar level well below normal and usually below 50 mg. per 100 cc. In all cases physical exercise depressed the blood-sugar level still further and increased and hastened the onset of symptoms. Food or glucose gave prompt relief.

Diagnosis

Our experience with these and with other patients in whom the possibility of an islet-cell tumor has been raised is in agreement with that of Whipple[3] and leads to the belief that when marked hypoglycemia with blood-sugar values below 50 mg. per 100 cc. regularly develops on fasting and is relieved by food, the presence of an islet-cell tumor must be assumed until proved otherwise, provided that by careful study extrapancreatic causes for the hypoglycemia have been excluded. These include diseases of the liver affecting glycogen storage and conditions associated with hypofunctioning of the adrenal cortex, the anterior lobe of the pituitary gland and the thyroid gland. Since conclusive evidence is lacking that the post-prandial hypoglycemia sometimes described in patients suffering from chronic fatigue[6] is due to excessive nervous stimulation of islet tissue, the term "hypoglycemia" rather than "hyperinsulinism" is to be preferred for this condition.

No elaborate diagnostic procedures are necessary. The characteristic symptoms associated with well marked hypoglycemia brought on by fasting, increased by physical exertion and relieved by food are the important features. As an aid in the diagnosis, the glucose-tolerance test is of value only if carried out for a sufficient length of time — that is for four to six hours. Characteristically, the fasting blood sugar starts at a low level — usually below 50 and frequently below 40 mg. per 100 cc. Following the administration of glucose, the rise in the blood sugar may be within normal limits or the curve may be diabetic in type. Conn and Conn[7] suggest that the type of curve depends on the amount of carbohydrate in the diet of the preceding few days; diets high in carbohydrate increase and those low in carbohydrate reduce sugar tolerance. The glucose-tolerance curve up to the third hour, therefore, may be essentially normal or mildly diabetic in type except for the initial value. After three hours, however, the blood sugar usually falls sharply to a low level (in 5 of the 6 cases reported above to approximately 40 mg. per 100 cc.) and in the fourth, fifth and sixth hours shows no tendency to rise spontaneously (Table 2). This last fact is significant: in normal persons one often obtains a hypoglycemic phase in the glucose-tolerance test but, presumably owing to the compensatory secretion of adrenaline, there is a spontaneous return to normal values. Such a return does not occur in

hyperinsulinism, probably because of the continuous secretion of insulin by the islet-cell tumor.

The glucose-tolerance curve in patients with hyperinsulinism differs from that described by Portis[6] in patients with hypoglycemia associated with vagotonia and fatigue in the following particulars: in the latter condition the fasting blood sugar, although perhaps lower than the average normal, is not depressed to the extent seen in hyperinsulinism; the curve tends to be flat; and the lowest blood sugar usually occurs two, three or four hours after the administration of glucose, and there is a tendency to return to normal without the administration of food or glucose.

Table 2. *Blood-Sugar Levels after Oral Administration of 100 gm. of Glucose.*

Case No.	Date of Test	Concentration before Test	Concentration after Administration of Glucose						
			½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
		mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
1	1/ 7/39	69	161	136	112	67	54	52	—
		*54**	*137*	*101*	*73*	*59*	*56*	*43*	—
	1/14/39	*45*	*190*	*296*	*238*	*162*	*80*	*46*	*48*
	2/10/39†	*95*	*188*	*159*	*132*	—	*119*	*81*	*92*
	6/ 1/39	*95*	*214*	*180*	*110*	*122*	*87*	*90*	*95*
2	6/22/39	36	121	102	80	—	40	38	39
		66	*147*	*123*	*103*	*70*	*61*	*60*	*56*
	7/18/39	—	140	140	120	100	50	70	—
		110	*160*	*190*	*140*	*100*	*90*	*80*	*100*
	10/18/39	89	130	118	77	—	56	—	75
		106	*164*	*146*	*111*	*123*	*97*	*75*	*92*
	5/22/40	90	115	100	73	54	66	72	81
	5/30/42	74	133	69	74	69	59	57	—
3	9/19/38	34	106	138	126	104	49	35	—
		35	*135*	*157*	*138*	*115*	*55*	*35*	—
	9/14/39	28	67	82	104	80	45	—	—
		34	*95*	*112*	*127*	*99*	*44*	—	—
4	9/27/40	25	92	166	208	196	100	72	47
	10/21/40	83	112	123	127	128	—	—	—
	10/25/40	—	96	110	135	91	111	102	96
5	10/15/40‡	35	123	110	100	87	58	31	—
	5/ 2/41‡	62	—	169	148	100	52	39	—
	7/11/41‡	43	123	160	170	138	80	—	—
	11/26/41	93	153	141	120	88	76	73	—
		95	*190*	*202*	*155*	*112*	*95*	*78*	—
6	11/14/41	—	118	166	134	115	68	57	—
		65	*133*	*190*	*156*	*132*	*75*	*59*	—
	12/ 5/41	78	137	—	106	78	63	88	—

*Figures in italics represent values obtained on capillary blood, the unitalicized figures representing those obtained on venous blood.
†On this date 80 gm. of glucose was given.
‡Tests performed at Duval County Hospital, Jacksonville, Florida.

Various secondary tests may be carried out, including blood-sugar studies following the giving of epinephrine, pituitary extract, ergotamine and insulin. One would expect the blood-sugar-raising effect of epinephrine and pituitary extract to be less and the blood-sugar-lowering effect of insulin to be greater than those in normal persons studied under the same conditions. This is true in general, but our experience has been that although the results obtained are interesting, they are apt to be variable and do not contribute significantly to the diagnosis. Table 3 shows the values obtained in such studies with our patients.

Location, Type and Size of Tumors

Although islet-cell tumors are said to occur most frequently in the tail of the pancreas, in these 6 cases the tumor was found in the head in 4 cases and once each in the body and tail of the pancreas. In 5 of the patients the tumor was an adenoma, more or less encapsulated, composed chiefly of beta cells. In 1 a carcinoma of mixed-cell type was present, with multiple metastatic nodules in the liver.

The tumors in the 6 patients were uniformly small nodules, varying from about 1 to 2 cm. in diameter, although in the patient with carcinoma several of the nodules in the liver were larger. Although most of the reported islet-cell tumors were small, averaging about 1.5 cm. in diameter, some were quite large. The one reported by Brunschwig,[8] which was 13 by 10 cm., and in its greatest diameter, 15 cm., weighed 673 gm. In the case reported by O'Leary and Womack[9] the growth was likewise quite large, measuring 11 by 9 by 9 cm. and weighing 500 gm. The tumor in Brunschwig's case was of especial interest, since because of a previous exploration it was known to have increased in size from about 7 to 15 cm. in diameter over a period of four months; nevertheless, and despite the fact that the tumor appeared malignant histologically, there was no gross evidence of metastasis at the time of the second operation.

Surgical Treatment

Once the diagnosis of a probable islet-cell tumor has been made, exploration should be urged, not only for symptomatic relief but also because of the possible danger of damage to the central nervous system produced by repeated attacks of prolonged hypoglycemia and because of the possibility of malignant degeneration of a tumor originally benign.

TABLE 1. *Data and Results of Treatment in 6 Cases of Pancreatic Islet-Cell Tumor.*

Case No.	Sex	Age at Onset of Symptoms	Age at Operation	Lowest Fasting Blood Sugar	Date of Operation	Location of Tumor	Size of Tumor	Type of Tumor	Insulin Content of Tumor	Encapsulation of Tumor	Blood-Vessel Invasion	Metastasis	Result of Treatment (1946)
		yr.	*yr.*	*mg./100 cc.*			*mm.*		*units/gm.*				
1	F	11	16	28	1/16/39	Head of pancreas	12 x 11 x 9	Adenoma	7	Incomplete	None	—	Patient symptom free
2	F	41	49	28	6/28/39	Body of pancreas	15 (diameter)	Adenoma	More than 100	Specimen unsatisfactory for examination	None	—	Patient symptom free
3	F	55	59	21	9/16/39	Tail of pancreas	18 x 18 x 13	Carcinoma (mixed-cell type)	—	Incomplete	Present	Multiple nodules in liver	Death on November 3, 1939
4	F	26	29	25	10/ 7/40	Head of pancreas	—	Adenoma	3	Incomplete	None	—	Patient symptom free
5	M	30	32	33	10/31/41	Head of pancreas	15 x 15 x 17	Adenoma	100	Incomplete	None	—	Patient symptom free
6	M	43	45	48	11/18/41	Head of pancreas	10 (diameter)	Adenoma	—	Incomplete	Questionable	—	Patient symptom free

TABLE 3. *Capillary Blood-Sugar Levels after Subcutaneous Injection of Various Drugs Prior to Operation.*

Case No.	Date	Drug Administered				Concentration before Test	Concentration after Injection of Drug							
		Epinephrine (1:1000)	Pituitary extract*	Unmodified insulin	Ergotamine tartrate (1:2000)		¼ hr.	½ hr.	¾ hr.	1 hr.	1¼ hr.	1½ hr.	1¾ hr.	2 hr.
		cc.	*cc.*	*units*	*cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
1	1/11/39	0.5				48	82	85	77	66	55	50	48	44
	1/12/39			2.0		50	45	44	46	43	—	—	—	—
	1/13/39		0.5			96	102	105	107	101	109	108	108	104
	1/13/39				0.2	62	53	50	51	50	—	—	—	—
	2/ 1/39†				0.4	138	127	114	101	104	—	—	—	—
	2/ 2/39†	0.5				97	147	168	192	199	205	204	177	160
	2/ 3/39†		0.5			63	67	68	67	68	69	65	65	64
	2/ 4/39†			6.6		99	—	89	—	75	—	75	70	66
2	6/20/39		1.0‡			47	49	49	49	49	46	—	—	—
	6/24/39	1.0				50	50	50	49	55	61	63	69	67
3	9/21/38	1.0				39	45	50	56	50	42	—	—	—
5	10/30/41	0.5				53	55	66	69	67	66	65	—	—
	10/30/41			7.0		89	82	77	56	53	47	46	—	—
6§	11/13/41			8.0		45	—	—	—	35	—	32	—	35

*Surgical double-strength extract was used (1 cc. = 20 i. u.).
†After operation.
‡Extract was injected intramuscularly.
§Venous blood was employed in the determination.

In reviewing the literature before 1944, Frantz,[10] working with Whipple, found a total of 149 cases of islet-cell tumor with hypoglycemia, including those removed at operation and those found at autopsy; 106 cases were shown to be benign, 28 were questionably malignant and 15 were proved malignant since there were metastases in adjacent organs.

Microscopic examination of tumor tissue from the 5 patients with adenoma showed the capsule of the tumor to be incomplete in each of the 4 cases in which enough tissue was available for satisfactory examination (Table 1). In 1 of the 5 cases, questionable blood-vessel invasion was noted. This is in keeping with the experience of Frantz,[11] who stressed the fact that great difficulty is often encountered in the histologic differentiation of malignant and benign islet-cell tumors. Usually, the tumors show encapsulation of varying degrees of completeness, but in some cases there is no capsule and tumor cells are found in the blood vessels. Certain patients from whom tumors of questionable type were removed, however, have remained alive many months after operation.[12] Frantz[10] states that in the group of questionable tumors the suspicion of the pathologist, not that of the surgeon, has yet to be confirmed in a single case by follow-up data. The suggestion is made that these tumors are analogous to the so-called "adenoma malignum" type of carcinoma of the thyroid gland, which is slow growing and late to metastasize. At any rate, there is sufficient basis for urging surgical exploration in any patient in whom the diagnosis of probable islet-cell tumor has been made.

Experience has shown that if, despite careful search, no tumor is found at operation, the possibility is nevertheless great that a small tumor has been overlooked. In most reported cases in which a portion of the pancreas has been resected and no evidence of tumor or adenomatosis found, little or no clinical improvement followed the operation.[10] It is well, therefore, to be cautious in making the diagnosis of functional hyperinsulinism — that is, hypoglycemia of chronic, recurrent nature due to hyperfunctioning of islet cells without the presence of a tumor. The term "hyperinsulinism" should be reserved for that condition in which excessive secretion of insulin occurs because of overactivity of islet tissue.

The approach to the pancreas through a long, curving transverse incision just above the umbilicus and through both rectus muscles has proved satisfactory. In the exploration one cannot overemphasize the value of freeing the pancreas thoroughly so that it may be palpated throughout its extent from the tip of the tail to the head, and so that it may be visualized over as large a part of its course as possible. This means that infinite pains and patience are required and that at times the operation will be long. Of our 6 patients, 2 had been operated on previously by competent surgeons and yet the tumor was overlooked. Palpation must be sufficiently thorough and delicate to disclose a tiny nodule embedded within the substance of the pancreas and not visible from either surface. If one is convinced of the diagnosis prior to operation, the exploration should be carried to the limit in an attempt to demonstrate a tumor. Even though one nodule has been found, the exploration should be continued because of the relatively high incidence of multiple tumors.[10, 13] In Maxeiner's[13] case clinical recovery from attacks of hypoglycemic seizures followed the removal of 75 per cent of the pancreas; examination of the resected portion showed eight small islet-cell tumors. If no tumor is found after careful exploration, decision must be made regarding resection of a portion of the pancreas. The consensus appears to be that resection under these circumstances should be of radical nature.[13, 14]

It is surprising how well patients withstand manipulation of the pancreas and removal of the tumors. With the exception of the patient who had a carcinoma with metastases, all our patients did well postoperatively. It is true that one patient developed bronchopneumonia, but the illness was not prolonged and he left the hospital in good condition a month after operation.

Summary

Six cases of islet-cell tumor of the pancreas with hyperinsulinism, verified at operation, are reported. In 5 cases, removal of a single adenoma resulted in the relief of symptoms that has persisted more than four to seven years after operation. In 1 case death followed seven weeks after operation, which disclosed an islet-cell carcinoma, with multiple metastases in the liver.

Of the 5 patients with benign adenoma 3 were women and 2 men. The ages at the time of operation ranged from sixteen to forty-nine years. The period from the onset of symptoms varied from two to eight years. In 4 cases the tumor was in the head and in 1 in the body of the pancreas. Two of these patients had been operated on previously without the discovery of a tumor.

The patient with carcinoma was a woman of fifty-nine years at the time of operation, with symptoms of four years' duration. In this case the primary tumor was in the tail of the pancreas.

Microscopic examination of tumor tissue from the 5 patients with adenoma showed the capsule of the tumor to be incomplete in each of 4 cases in which there was enough tissue available for satisfactory examination. In 1 case questionable blood-vessel invasion was noted.

In the 4 cases in which assays were carried out, the insulin content ranged from 3 to over 100 units per gram of tumor tissue.

The important features in the diagnosis of islet-cell tumor are the characteristic symptoms associ-

ated with well marked hypoglycemia (blood-sugar concentrations usually below 50 mg. per 100 cc.) brought on by fasting, increased by physical exertion and relieved by food. The glucose-tolerance test is of aid in diagnosis only if carried out for a sufficient length of time — that is for four to six hours — to allow the blood sugar to fall to an abnormally low level.

Because of the danger of damage to the central nervous system by repeated attacks of prolonged hypoglycemia and because of the possibility of malignant degeneration of a tumor initially benign, early exploratory operation is urged in patients in whom the diagnosis of islet-cell tumor with hyperinsulinism has been made.

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UNRECOGNIZED VESICAL-NECK OBSTRUCTION IN WOMEN*

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MOST urologists are aware of the fact that vesical-neck obstruction in women exists, but not all, I believe, are aware of the fact that it is not an infrequent entity. Although no statistics are available regarding its incidence the condition undoubtedly occurs oftener than is ordinarily appreciated, and I have seen 4 advanced cases in the last two years. Caulk[1] (1921), Nesbit[2] (1933), Fite[3] (1934), Thompson[4] (1935) and van Houtum[5] (1935) reported 1 or more cases, and Mirabile[6] presented a case in 1942. The principal reason for the presentation of the following cases is not only to call attention to this condition again but also to urge that it be recognized early and that its treatment be instituted early enough to avoid the late sequelae of such obstruction. The word "unrecognized" is used to indicate that this condition may easily be overlooked during the routine urologic examination of the patient.

The following brief summaries illustrate the important findings in 3 cases of vesical-neck obstruction in women.

Case 1. (H. H. 471-447). L. S., a 71-year-old married woman, had had severe urgency, dysuria, frequency and nocturia as often as 10 to 15 times of several months' duration. Prior to this, and for as long as she could remember, she had had difficulty starting urination and had had to get up several times nightly. A stone had been removed from the lower right ureter 4 months previously, with no improvement in the symptoms.

Urinalysis revealed moderate pyuria, and on urinary culture *Aerobacter aerogenes* was grown. On several determinations the residual urine ranged from 600 to 700 cc. Cystoscopy disclosed a large, moderately trabeculated bladder, with an iris-type contracture of the vesical neck and two diverticulums

Figure 1. *Case 1: Cystogram showing a large atonic bladder, with two diverticulums.*

in the right base of the bladder. A cystogram showed a large, atonic appearing bladder, with two diverticulums (Fig. 1). A urogram revealed mild pyelectasis and a hydroureter on the right. The left kidney and ureter appeared normal.

A partial sphincterectomy was performed, 2 gm. of tissue from the posterior vesical lip being removed. Pathologically the tissue consisted of smooth muscle and transitional epithelium.

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The residual urine gradually diminished, and within 2 weeks all symptoms had subsided.

CASE 2. (H. H. 484-675). B. W., a 74-year-old spinster, had been troubled with urgency, dysuria, recurring hematuria, frequency and nocturia of 4 to 10 times as long as she could remember. Urologic examination 3 years previously had revealed "chronic alkaline-encrusted cystitis," and vesical lavage had been advised. Cystoscopy at that time had revealed trabeculation and cellules.

Urinalysis showed grossly turbid, hemorrhagic urine containing *Proteus ammoniae*. The residual urine varied between 90 and 100 cc. Cystoscopy disclosed a markedly trabeculated

FIGURE 2. *Case 2: Cystogram showing a pyramidal trabeculated bladder, with many cellules.*

bladder, with many cellules and diffused cystitis. The bladder neck was rigid and contracted. A cystogram demonstrated a pyramidal, trabeculated bladder, with many cellules (Fig. 2). Normal upper urinary tracts were seen on a urogram.

A total internal sphincterectomy was performed, 5 gm. of tissue being removed from the entire circumference of the vesical neck. Pathological examination revealed tissue composed of smooth muscle and fibrous tissue, with a border lined with stratified squamous epithelium.

Within 6 weeks the residual urine had diminished, and the symptoms were markedly ameliorated.

CASE 3. (H. H. 528-588). A. H., a 73-year-old married woman, complained of hematuria of 3 weeks' duration. Six years previously she had had hematuria, and complete urologic investigation had revealed only cicatricial urethritis. She had also suffered for several years with severe dysuria, mild stress incontinence, frequency and nocturia of 6 times.

On urinalysis moderate pyuria and gross hematuria were demonstrated. On culture *A. aerogenes* was grown. There was approximately 100 cc. of residual urine. At cystoscopy the bladder was badly deformed, with multiple cellules and marked trabeculation and dilated ureteral orifices. The vesical neck was rigid and contracted. A moderate cystocele was present. A cystogram revealed a pyramidal bladder with marked trabeculation and multiple cellules in the apex of the pyramid (Fig. 3). The base of the bladder was smooth, suggesting the presence of a cystocele. Bilateral ureteral reflux demonstrated a bilateral hydroureter. A urogram showed bilateral hydronephrosis.

A single section of tissue was resected at the midportion of the posterior vesical neck, followed by dilatation of the urethra. On pathological examination the fragment of the vesical neck consisted of thickened and edematous mucosa,

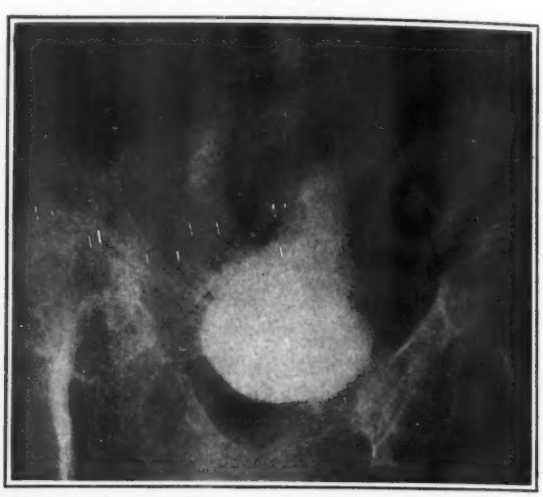

FIGURE 3. *Case 3: Cystogram showing a pyramidal bladder, with marked trabeculation and multiple cellules in the apex of the pyramid, as well as a cystocele and bilateral ureteral reflux and hydroureters.*

with chronic inflammatory changes in the submucosa. Several small foci of epithelium present below the surface were slightly cystic and suggested cystitis cystica.

The hematuria subsided and the patient's symptoms improved greatly. Nocturia of 2 times persisted. The residual urine diminished to 10 cc.

The advanced ages of these patients and of another patient not reported indicate that in women this condition is usually present in the older age groups, as it is in men. Of the cases reported in the literature the greatest number were in this same age group. "Prostatism *sans* prostate" seems a particularly appropriate term to describe this group of cases.

The etiology of vesical-neck obstruction in the female is not definitely established. Perhaps the most popular theory is that the obstruction is due to a contracture of the vesical neck resulting from sclerosis or fibrosis at this site, the fibrosis being attributed to chronic low-grade inflammation of the urethra or to vaginal trauma. Some observers believe that the contracture is due to hypertrophy of the muscle fibers at the vesical neck and is not the result of cicatrization at this site. Another point of view is that the obstruction is fundamentally physiologic and due to dysectasia or achalasia — in other words, to a failure of the vesical neck to relax as the bladder contracts. This theory implies that the innervation of the bladder and vesical neck is at fault, and an imbalance between the sympathetic and the parasympathetic innervations is considered responsible.

In the light of present knowledge no one explanation is completely satisfactory. Although the theory of fibrosis of the vesical neck seems plausible enough,

it is disconcerting to note that the amount of fibrous tissue found at autopsy in the vesical neck of a series of normal women was similar to that observed in a series of cases of vesical-neck obstruction subjected to transurethral surgery. Furthermore, it seems reasonable to assume that if chronic infection and its accompanying cicatrization were factors the obstruction would be seen much oftener than it is. According to Thompson[4] it seems almost certain that something other than fibrosis is responsible for the retention of urine in these cases. The theory of imbalance between the sympathetic and parasympathetic innervations of the bladder has also been questioned of late as a result of recent experimental work that has tended to minimize the importance of the sympathetic innervation. In experimental studies the sympathetic innervation was completely excised, with little, if any, alteration in the animal's ability to void. In keeping with this change in the concept of the physiology of micturition the theory of imbalance has received less support.

The presence and the significance of the urethral glands — the so-called "female prostate" — in the development of chronic vesical-neck obstruction has been the subject of much discussion. There is no question that such glands do exist and, when enlarged, actually cause mechanical obstruction or, as is more frequently observed, influence the chronicity of the urethritis and contribute to the resulting cicatrization of the urethra and vesical neck. Although the glands are undoubtedly involved in some cases it is my impression that their role is minor. Questionable glands were present in only 1 of my 4 cases.

The symptoms of chronic vesical-neck obstruction in women are similar to those in men. Urination may be difficult to initiate, or urgency to the point of incontinence may be present. Dysuria, which is usually observed, may be associated with vesical tenesmus and strangury. Frequency and nocturia are usually marked and generally constitute the chief complaints. Recurring hematuria was present in 2 of the cases presented above. The symptoms are usually of long duration; 2 of the 3 patients complained that voiding had been abnormal all their lives. Chronic cystitis is the diagnosis usually made in these cases.

In addition to the general physical examination a careful neurologic and vaginal examination should be performed to exclude the presence of neurogenic vesical dysfunction and to rule out such complicating factors as cystocele, urethral diverticulum and urethral tumor.

The urologic examination should include a routine urinalysis, determination of the residual urine and a careful cystoscopic examination. A cystogram is helpful. Examination of the upper urinary tracts is sometimes quite revealing. Cystometry, although interesting, was not particularly illuminating or helpful in my cases.

Urinalysis reveals a pyuria of greater or lesser extent, and urine culture yields the usual microorganisms found in lower urinary-tract infections. Microhematuria may also be present.

Determination of the residual urine is perhaps the most significant single test that is made. This is particularly true in cases in which the cystoscopic findings are minimal or inconclusive. If residual urine is present resection of the vesical neck is indicated.

The cystoscopic findings in the advanced cases are usually obvious. Marked trabeculation, cellule formation, sacculation and diverticulums may be present, and all suggest the presence of vesical-neck obstruction as they do in men. The vesical neck itself appears to be contracted and is usually pale, suggesting the presence of cicatrization; it is also rigid and relatively fixed in position. Median-bar formation may be prominent or, as is most frequently observed, an iris-diaphragm type of contracture is present in which the internal vesical orifice actually diminishes in size as the bladder is distended. Cystoscopic visualization of the vesical neck is best performed with a direct-vision cystoscope or, if this is not available, with a for-oblique lens system. The use of a retrograde lens is helpful in that the obstruction may occasionally be more readily recognized from the vesical rather than a urethral aspect.

Early vesical-neck obstruction is difficult to recognize and usually escapes detection. The cystoscopic findings are minimal and at most may consist only of early trabeculation. The vesical neck may or may not appear to be contracted, and there is no residual urine. The most significant finding in my experience is the presence of rigidity in the vesical neck that is discernible when the bladder is completely empty and flaccid. A suspicion of early vesical-neck obstruction is probably the best assistance in its diagnosis.

The ideal treatment in cases of contracted vesical neck consists in removing all the obstructing tissue or in resecting the entire vesical neck or so-called "internal vesical sphincter." Although this procedure is ideal it is not always necessary, and resection of the posterior vesical lip or median bar is frequently all that is required. Sphincterotomy or incision of the posterior vesical lip, although helpful, is usually of only temporary benefit. Urethral dilatation is the least desirable form of treatment. Following the resection an indwelling catheter is left in for forty-eight to seventy-two hours, after which frequent catheterization and vesical lavage may be necessary to facilitate the return of vesical tone and the elimination of residual urine. Eradication of the urinary-tract infection may be helped with chemotherapy.

Summary

Three cases of chronic vesical-neck obstruction in women are presented in which resection of all or part of the vesical neck was performed with satisfactory relief of symptoms.

Attention is drawn to the facts that the condition is not infrequent and that dire consequences, in the form of dilatation of the upper urinary system, may ensue if treatment is not instituted early in the course of the disease.

A search for the presence of early vesical-neck obstruction in every case of chronic cystitis in women is urged, so that this condition may be recognized and adequate treatment instituted.

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RETROPERITONEAL HEMORRHAGE COMPLICATING PREGNANCY*

Report of a Case

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BOSTON

In 1918 Potocki[1] reported a case of retroperitoneal hemorrhage complicating pregnancy in which the patient, two and a half months' pregnant, experienced pain in the lower abdomen after intercourse. The pain extended gradually to the left side, with some degree of shock. Shortly after admission to the hospital the pain became severer and the shock deeper. The diagnosis was ruptured tubal pregnancy or pregnancy with an ovarian cyst with a twisted pedicle. Laparotomy performed immediately revealed an extensive retroperitoneal hemorrhage that did not involve the true pelvis but filled the mesocolon and the retroperitoneal areas in the region of the pancreas, left kidney and stomach. The patient died on the operating table. Autopsy did not disclose the bleeding vessel. It was concluded that a major vessel had perforated because 1200 to 1800 cc. of blood was present retroperitoneally. The left kidney was found to be tuberculous, and a large hematoma surrounded the kidney. Potocki believed that the probable cause of the hemorrhage was a miliary aneurysm of the renal artery. His search of the literature failed to reveal any other case occurring in pregnancy, but disclosed similar cases in men, one of which was a spontaneous fatal hemorrhage from a psoas-muscle vessel. In another case severe pain developed in the left side of the abdomen, and a mass could be felt in the left renal region; the patient died on the operating table, and post-mortem examination revealed a large retroperitoneal hemorrhage, small abscesses in the kidney and stones. A third patient, who had syphilis, died of a cerebral accident, and autopsy disclosed a large retroperitoneal hemorrhage that was believed to have started from the renal artery, since there was a history of an old perirenal abscess. Potocki concluded that pregnancy did not predispose a patient to this condition and believed that in most cases the hemorrhage started from renal vessels.

Low,[2] in 1944, reported a fatal case in pregnancy. The patient, within two weeks of term, was admitted to a hospital several hours after being seized with violent pain originating in the left upper quadrant of the abdomen and extending to the back. The pain occurred after a bowel movement, and shock ensued shortly after its onset. A transfusion was given, and a classic cesarean section was performed. A moderate amount of blood-stained fluid was found in the abdomen, but the essential finding was a massive retroperitoneal hemorrhage extending from above the left brim of the true pelvis and behind the sigmoid, descending colon and splenic flexure, across the midline of the upper abdomen and apparently most marked in the region of the spleen and left kidney. The patient died seven hours after operation, in spite of another transfusion. Postmortem examination revealed all the large arteries to be relatively thin walled, and the left ovarian artery to be particularly so, as well as dilated and tortuous and presenting some aneurysmal dilatation near its origin. Kenny,[3] in 1945, reported a similar case in which the patient, who had preeclampsia and was at term, had pain and shock following intercourse. A retroperitoneal hemorrhage extending from the pelvic brim to the diaphragm was discovered. The source of the bleeding was not found at autopsy. Kenny believed that the source of the hemorrhage was the retroperitoneal capillaries.

Wilson[4] delivered normally at full term a patient who twenty-six hours post partum experienced

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severe pain and collapsed. She died on the operating table. An aneurysm of the left renal artery was discovered. Eiss,[5] who reported 2 fatal cases of retroperitoneal hemorrhage in men, stated that the differential diagnosis in women must include the following: ectopic pregnancy, perforated gastric ulcer, appendicitis, and if trauma is a factor, a ruptured viscus. He believed that there must be prompt exploration to find the cause. When the hemorrhage is retroperitoneal the abdomen should be closed immediately and the shock treated. He stated that a careful search of the literature revealed only 7 cases similar to the 2 he reported. Läwen[6] also reported 2 fatal cases in men. One patient had a preoperative diagnosis of left perirenal hemorrhage, and a retroperitoneal operation was performed. Autopsy revealed a large left retroperitoneal hemorrhage from a perforation of the inferior vena cava at its junction with the left common iliac vein. There was a chronic inflammatory infiltration of the wall of the vein (phlebitis dissecans) and also an old thrombophlebitis, which he believed secondary to a chronic knee condition. The other patient had right renal colic, and the preoperative diagnosis was retroperitoneal tumor. Extraperitoneal operation revealed a cyst containing 1000 cc. of old blood. The cyst wall was formed probably by organization of the peripheral parts of the hematoma. The kidney, as part of the wall, was removed. Seven weeks after operation the patient collapsed. A large cavity filled with blood, which was found after entry through the old incision, was emptied and packed. The patient finally died of pulmonary embolism. Post-mortem examination revealed sarcoma of the lumbodorsal fascia, with metastases scattered in various areas.

Halban[7] believed that a retroperitoneal hemorrhage is nearly always perirenal at the start, that it may be secondary to tuberculosis or tumor of the kidney and that it may also occur spontaneously in nephritis and hemophilia. He stated that the bleeding caused by trauma, tuberculosis and tumor is of no special interest but that the spontaneous essential hemorrhages, in spite of many observations, have not yet been fully explained.

The following case report is unique in two respects: it is the only case of retroperitoneal hemorrhage complicating pregnancy with recovery that has been reported, and describes for the first time a new entity causing dystocia.

Case Report

B. F., a 38-year-old woman, had been married for 12 years. A child, weighing 6 pounds, 12 ounces, had been born 11 years previously; the pregnancy, delivery and convalescence had been normal. The past history revealed an appendectomy at the age of 26 but no serious medical illnesses. The menstrual history was normal. The patient's father and mother and three siblings were living and well; there was no history of the usual familial diseases. The last menstrual period had begun on February 2, 1945, and confinement was expected on November 24.

Physical examination was negative. On the first visit on June 5 the uterus, which was enlarged about two thirds the way to the umbilicus, seemed slightly firmer than usual. The impression was gained that the uterus was slightly larger than the dates indicated, but the patient was not absolutely sure of the date of the last catamenia. The weight was 140 pounds. The blood pressure was 150/90, and the pulse 80. Examination of the blood revealed a red-cell count of 4,010,000, with a hemoglobin of 72 per cent (Sahli). The blood was of Group 0 and was Rh−. The blood Hinton reaction was negative.

The patient had an uneventful pregnancy. Vaginal examination on November 17, approximately a week before the expected date of confinement, revealed a cervix that was partly taken up and soft and slightly anterior to the usual position. It admitted a finger readily. The presenting part, however, was not definite. On December 1 the patient was admitted to the Cambridge Hospital because of moderate pain in the left side. Physical examination revealed slight tenderness along the course of the ureter; there was no costovertebral tenderness. The uterus was soft, and the fetus appeared to be slightly less than average size. The temperature was 99.2° F., and the pulse 92. A catheterized specimen of the urine was taken; the report of the sediment was equivocal — there were said to be 40 or 50 white cells per high-power field. An anteroposterior film revealed a fetus of a size consistent with an 8 months' pregnancy and in a left occipitoanterior position; the head was unusually high. Vaginal examination revealed a tender, moderately firm mass filling the posterior part of the pelvis and pushing the cervix up behind the symphysis. The diagnosis was probable fibroid of the lower segment of the uterus causing dystocia. Cesarean section was deemed advisable.

At operation on December 5, under continuous spinal anesthesia employing 6 mg. of pontocaine, the usual midline incision was made below the umbilicus and the abdomen was opened. A small amount of blood was found in the left side of the lower abdominal cavity. The bladder flap, which was somewhat soggy and thin, was stripped from the uterus, and a transverse incision was made in the lower segment. A female infant weighing 5 pounds, 6 ounces, was extracted. The uterus was brought out of the incision for examination of the abdomen. Whereas previous to the incision in the uterus, the examiner's hand had been passed around the uterus without palpating a fibroid, inspection revealed a large, firm, retroperitoneal hemorrhage that filled the whole true pelvis and extended well into the mesentery of the sigmoid, which was ribboned out over the hemorrhagic mass. The diagnosis was retroperitoneal hemorrhage in the true pelvis causing dystocia. It was decided that the best treatment was to leave the hemorrhagic area undisturbed. The placenta had been delivered while the character and extent of the mass were being investigated. The uterus was closed with No. 1 catgut in two layers. Five grams of sulfanilamide was placed under the bladder flap, which was overlapped with a fine stitch. The abdomen was closed in layers, No. 1 chromic catgut being used for the peritoneum and fascia and silk for the skin.

There was no excessive bleeding from the incision or the uterus, and the postoperative condition was good. On December 6 the temperature was 100.6° F., and the pulse 106 to 130. Distention was slight. Rectal examination revealed that the mass could be readily felt and was still tender. Two days later the temperature varied from normal to 99.2° F. There was no distention. The general condition was good. On December 14, when the patient was allowed to sit up, the temperature still varied from normal to 99.2° F. Otherwise, the general condition was excellent. The patient was discharged on the 13th day.

Pelvic examination on February 23, 1946, revealed a slightly tender, firm mass — about 3 cm. in diameter — posterior to the cervix but not projecting far into the vagina. The hematoma was evidently being absorbed slowly. There was slight to moderate discomfort in the left lower abdomen. On May 20, when the patient still complained of vague back and lower abdominal discomfort, examination revealed slight tenderness behind the cervix, but the hematoma, which was smaller, was palpated with difficulty.

Summary

Retroperitoneal hemorrhage complicating pregnancy is extremely rare but probably occurs more frequently than reports indicate. One type is characterized by severe abdominal pain and shock as a

result of massive retroperitoneal hemorrhage in the upper abdomen. The most frequent source of the hemorrhage is disease in the kidney and its vessels. The condition is usually fatal. The other type, reported above for the first time, is a retroperitoneal hemorrhage occurring chiefly in the true pelvis and resulting in a tumor causing dystocia and necessitating cesarean section.

The source of the hemorrhage in the case reported was probably one of the hemorrhoidal veins. Such a hemorrhage should not be evacuated; its complete absorption may take months.

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THE EFFECT OF AGE ON THE CLINICAL EFFECTIVENESS OF NITROGLYCERIN TABLETS*

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BOSTON

THE value of sublingual administration of nitroglycerin for relief of attacks of angina pectoris is well established. Nitroglycerin has also been advocated as a prophylactic — before exercise and so forth — to prevent pain.[1-3] Objective measurements of the value of both these therapeutic uses have been reported.[2, 4, 5]

From a practical point of view, the stability of nitroglycerin tablets is important. In the past, many lots of nitroglycerin have been condemned as substandard, presumably because of deterioration. As a result, fresh tablets are recommended, to be dispensed in tightly stoppered bottles.

The question of deterioration of nitroglycerin is still controversial. No definite standards of freshness have been established, and no simple methods of analysis are available. None of the numerous procedures of chemical or biologic assay used for testing the deterioration of nitroglycerin yield information concerning the most significant clinical aspect — namely, the efficacy in the treatment of angina pectoris. This aspect can be measured readily by determining the exercise tolerance, under carefully standardized conditions, of patients with and without the use of nitroglycerin at varying periods after manufacture.

The purpose of this communication is to report the effect of age and heat on the clinical effectiveness of hypodermic tablets of nitroglycerin as determined in patients with angina pectoris. Only hypodermic tablets were tested because attacks of angina pectoris are short in duration, and hence rapidly dissolving hypodermic tablets are preferable to triturated ones.[2, 3]

The various chemical methods that have been proposed for quantitative analysis of the small amounts of nitroglycerin present in medicinal preparations have been summarized by Hutchinson.[6] In general, they consist of extraction of the nitroglycerin, its reduction into one or more of its breakdown products (nitrogen, nitrate salts, nitrite salts or ammonia), determination by colorimetric or gaseous analysis of the amount of this product and computation therefrom of the amount of nitroglycerin present in the original preparation. The official assay method of *U. S. P. XII*, for example, consists of repeated ether extraction of no less than twenty finely powdered nitroglycerin tablets, evaporation of the ether and saponification of the nitroglycerin in the presence of potassium permanganate. Devarda's alloy is then added to the mixture, and the nitrate present is thereby reduced to ammonia. This is distilled into a standard solution of sulfuric acid, and the amount of unneutralized sulfuric acid is determined by titration with sodium hydroxide, methyl red being used as an indicator. The amount of nitroglycerin originally present is computed from these figures. Blank determinations with the same quantities of reagents are performed in a similar manner, and the necessary corrections made.

Deterioration of nitroglycerin tablets with age has been investigated by chemical determination of the nitroglycerin content at varying times after manufacture. The results, however, are controversial. Scoville,[7] Smith[8] and Meek[9] found significant loss of nitroglycerin in tablets assayed up to four years after manufacture, whereas Bergenau,[10] Rippetoe and Smith,[11] Vanderkleed,[12] Snyder[13] and Francis[14] reported no significant loss in tablets assayed at periods up to eight years after manufacture.

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The divergent results were due in some degree to the unreliability of the chemical methods available. Technical difficulties arising from the small amounts of material used, impurities in the framework of the tablets and errors arising from colorimetric analysis are a few of the factors that contributed to the unreliability of these reports.

The fall in blood pressure in anesthetized rabbits after intravenous administration of small amounts of nitroglycerin was utilized as a method of biologic assay for nitroglycerin deterioration by Edmunds and Roth.[15] On the basis of their findings they concluded that tablets not more than two years old had lost practically none of their strength but that older tablets had deteriorated to some extent.

Although the results of chemical and biologic assay methods when applied to the question of deterioration of nitroglycerin with age have not been conclusive, it is generally believed by pharmaceutical manufacturers and clinicians that nitroglycerin is not a stable preparation. Accordingly, current medical opinion, as expressed in leading textbooks of cardiology and general therapeutics, recommends that patients employing nitroglycerin for the treatment of angina pectoris discard old tablets and purchase fresh ones every three to six months.

Material and Methods

The clinical potency of readily soluble hypodermic tablets of nitroglycerin of varying age in doses of 0.6, 0.4, 0.3, and 0.1 mg. (1/100, 1/150, 1/200 and 1/500 gr.) were investigated. Fifteen different preparations were tested. Three were fresh tablets (less than two months old). Three others had been on the laboratory shelves in pasteboard pillboxes for periods ranging from three to five years. Five were obtained from the shelves of retail drugstores and pharmaceutical houses, where they had remained for four to eleven years; no special precautions against deterioration had been taken in packaging and storage. Three samples originally less than two months in age were kept in pasteboard pillboxes in an incubator at 37° C. for three additional months to ascertain the effect of heat on their clinical effectiveness. The remaining sample consisted of fresh readily soluble hypodermic tablets (0.3 mg.) that had been kept in a loosely fitting screw-cap vial and carried by 2 patients for four months close to the body in the same vest or trousers pocket used for carrying their clinical supply of nitroglycerin.

Five male patients with angina pectoris, who had demonstrated a moderate to marked response following sublingual administration of nitroglycerin, were selected for these studies. The patients had been followed in a special clinic at weekly intervals for periods ranging from six months to eleven years. The amount of exercise each patient could perform before developing an attack of angina pectoris, as demonstrated by the standardized exercise tolerance test, had been determined on many occasions according to a method previously described.[16] The exercise, which consisted in mounting and descending a two-step staircase in a room maintained at a temperature of 45 to 50° F., was carried out approximately an hour after the patient had had a light breakfast and had rested for half an hour in the clinic. Only one test was attempted on any given day. The number of trips each patient could perform gave a measure of the exercise tolerance. During the period of study the patients were given only placebo medication except for nitroglycerin as needed in their everyday activities.

The exercise tolerance as determined on many occasions without medication was used as the control for the subject concerned. As a further check the exercise tolerance was measured two minutes after the sublingual administration of blank hypodermic tablets indistinguishable in appearance from the nitroglycerin used in the study. The results were compared with those ascertained two minutes after sublingual administration of fresh and old (three to eleven years old) tablets of nitroglycerin.

The amount of exercise necessary to induce angina, under the standardized conditions of the test when either no medication or blank hypodermic tablets were administered, varied in all but 1 case between 5 and 17 per cent of the average exercise tolerance for the patient. The clinical effectiveness of nitroglycerin was indicated by an increase in exercise tolerance of 25 to 100 or more per cent over the maximum amount of work possible under the control conditions.

Results

The sublingual administration of fresh hypodermic tablets of nitroglycerin prior to exercise increased the exercise tolerance of each patient by 25 to 100 per cent or more (Table 1). The increment of exercise induced by each preparation of nitroglycerin was essentially the same, despite a dosage range of 0.6 to 0.1 mg., except in a patient (L. S.) who showed a moderate response only to a dose of 0.6 mg. In 2 cases, after the administration of nitroglycerin, the patients were able to exercise to the point of fatigue or development of leg pain without precipitating angina pectoris.

Sublingual administration of blank hypodermic tablets did not result in an increase of ability to work.

The exercise tolerance following the administration of eight different samples of nitroglycerin three to eleven years old was the same as that following fresh nitroglycerin, regardless of the age of the tablets and the lack of special precaution in packaging and storage. The rate at which the tablets dissolved under the tongue was also unaffected by age, since all patients reported that each tablet dissolved in from ten to thirty seconds after the sublingual administration. Similarly, the speed of response was unaffected by age, for all tests were conducted two

minutes after sublingual administration of the tablets.

The tablets that had been stored in pasteboard pillboxes in the incubator at 37° C. for three months showed complete loss of clinical potency. The amount of exercise each patient could perform after sublingual administration of these tablets in dosages of 0.6, 0.3 and 0.1 mg. was essentially the same as that performed without medication or following administration of blank hypodermic tablets.

The tablets that had been carried close to the body for four months showed no loss of clinical potency.

Table 1. *Effect of Nitroglycerin on Patients with Angina Pectoris as Measured by Exercise Tolerance Test (in Trips).*

Patient	No Medication	Blank Tablets	Fresh Nitroglycerin Tablets			Old Nitroglycerin Tablets*							Incubated Nitroglycerin Tablets			Nitroglycerin Tablets Carried in Pocket
							3–5 yr. old		4 yr. old	5 yr. old	9 yr. old	10 yr. old	11 yr. old				
			0.6 mg.	*0.3 mg.*	*0.1 mg.*	*0.6 mg.*	*0.3 mg.*	*0.1 mg.*	*0.4 mg.*	*0.6 mg.*	*0.6 mg.*	*0.1 mg.*	*0.4 mg.*	*0.6 mg.*	*0.3 mg.*	*0.1 mg.*	*0.3 mg.*
E. B.	16–22	18–24	28†	29†	37†	29†	28†	37†	30†	30†	27†	34†	26†	24	22	23	23†
S. R.	26–30	28	56	55	47	59	47–61	51	54	56	50	46	60	32	30	30	56
S. W.	24–30	24	45†	50†	49†	50†	52†	47†	42†	52†	46†	45†	48†	31	30	30	35†
B. H.	17–18	20	42	63	49	63	60	49	55	60†	70†	42	53†	25	19	18	60†
L. S.	18–20	17	25	20	21	27	16	22	17	30	27	20	17	14	19	18	34

*Tablets stored in following types of containers: pasteboard pillboxes; brown screw-cap bottles; clear screw-cap jars; and clear tablet vials with cork stoppers.

†Exercise stopped because of fatigue or intermittent claudication, not angina pectoris.

Discussion

Direct transference of the results of chemical or biologic assay methods to the problem of clinical potency of old nitroglycerin preparations is not justifiable. It has been shown that for all practical purposes 0.3 mg. is as effective as larger doses and, furthermore, that tablets containing as little as 0.1 mg. of nitroglycerin are of clinical value.[2, 3] A decrease in the nitroglycerin content of old tablets, therefore, may not indicate a corresponding reduction of clinical value in patients with angina pectoris.

The clinical response following sublingual administration of nitroglycerin in 4 patients was essentially the same in dosages ranging from 0.6 to 0.1 mg. On that basis it might be postulated that old tablets of 0.6 mg. could lose up to 80 per cent of their nitroglycerin and still retain clinical potency and value. To determine if this were so, the nitroglycerin content of several 0.6-mg. tablets employed in this investigation was determined by the *U. S. P.* method of chemical assay (Table 2). Comparison of the content of the three old samples with that of the fresh tablets showed no significant loss of nitroglycerin. Furthermore the results in a patient (L. S.) who responded to 0.6 mg. but not to a dose of 0.4 mg. or smaller indicate that 0.6-mg. tablets as old as nine years failed to deteriorate appreciably in clinical value.

The method of biologic assay employed in this investigation gave a measure of the clinical effectiveness of the preparations tested regardless of their actual nitroglycerin content. This method, which has been used in this clinic for over ten years, has been found to offer a satisfactory objective measure of the effect of various medications in patients with angina pectoris.[17, 18] By employing the patient himself as a means of testing clinical efficiency the procedure avoids the difficulties that are inherent in the chemical or biologic methods of assay previously employed.

With the exception of the tablets exposed to heat, all preparations, regardless of age, showed no loss of clinical potency. These results indicate that, under ordinary conditions of storage in a retail drugstore, hypodermic tablets of nitroglycerin retain their clinical effectiveness for many years. Furthermore, under ordinary conditions of use by patients, they retain their effectiveness for at least four months. Therefore, it is not necessary for patients to purchase fresh supplies at more frequent intervals.

Table 2. *Chemical Assay of Four Preparations of Nitroglycerin.**

Age of Tablets	Percentage of Original Nitroglycerin Content
Fresh	104
Three to five years old	103
Five years old	78†
Nine years old	99

*These analyses were carried out by Dr. Bibbins, of the Pharmaceutical Department of Eli Lilly and Company, without knowledge of the age or the manufacturer of the four specimens.

†These tablets were soft, and the edges had worn off.

Tablets exposed to heat, however, rapidly lose their clinical effectiveness. This fact should be kept in mind when nitroglycerin preparations are stored. The tablets do not lose their clinical potency if kept at room temperature, but if they are kept near steam pipes, radiators and so forth, they are apt to suffer deterioration.

Summary

The clinical effectiveness in patients with angina pectoris of eleven preparations of hypodermic tablets

of nitroglycerin, in dosages ranging from 0.6 to 0.1 mg., were assayed at periods varying from a few months to eleven years after manufacture. No particular precautions against deterioration had been observed in the packaging and storage of these tablets. There was no essential loss of clinical effectiveness in the old tablets as compared to fresh tablets of the same dosage.

Fresh tablets exposed to heat (37° C.) for three months showed a complete loss of clinical potency, whereas tablets that had been carried by patients in the customary manner for four months showed no loss of clinical effectiveness.

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MEDICAL PROGRESS

THE DIAGNOSIS OF CANCER OF THE PANCREAS*

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BOSTON

TEN years ago Clute[1] discussed the problems presented by the diagnosis and treatment of cancer of the pancreas. In the intervening decade surgical treatment has progressed remarkably,[2–4] but diagnosis is still lagging, partly owing to the variability of pancreatic symptoms, the inaccessibility of the pancreas to examination, the difficulty of x-ray study of this gland and the unavailability of an easy and reliable function test. On the other hand, failure to recognize the symptoms that have been repeatedly emphasized in the literature of the last ten years and to institute such tests as have been made available are also responsible for the late recognition of pancreatic carcinoma.

The intimate anatomic relation of the head of the pancreas to the ampulla of Vater and its adjoining structures (the papilla of Vater, the terminal common bile duct, the duct of Wirsung and the duodenal mucosa covering the papilla) makes the exact site of origin of many cancers in this area uncertain. Although occasionally possible, the clinical differentiation between cancers of the pancreas and those of the ampullary region is particularly difficult. Any clinical consideration must consequently encompass neoplasms arising at both sites. Cancers of the islands of Langerhans, on the contrary, are characterized by a different syndrome and are not included in this discussion.

The literature as reviewed by Leven[5] in 1933 indicated that cancer of the pancreas afflicts the usual cancer age group between forty and seventy, attacks men two or three times as frequently as women and occurs roughly once in every thousand hospital admissions. Berk's[6] extensive review in 1941 confirmed these figures. He was also led to conclude that "carcinoma of the pancreas causes 1 to 2 per cent of all deaths in the population at large," a somewhat puzzling statement because Berk at the same time agreed with previous writers that cancers of the pancreas account for 1 to 2 per cent of all cancers. Since the publication of Berk's review, a number of articles have dealt with the incidence of pancreatic carcinoma,[7–13] but no trends have been observed that challenge the principal conclusions reached by Leven and Berk. It is to be noted, however, that youth provides no guarantee against pancreatic neoplasm. In 113 cases collected in two series 6 patients were under the age of forty,[7, 13] and up to 1941, pancreatic or periampullary cancer had been reported nine times in patients less than twenty years old.[9] Periampullary carcinoma, in particular, may appear in younger persons.[14]

Although opinion regarding the general incidence of pancreatic carcinoma is quite consentaneous, statements on the relative incidence of cancers of the

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ampullary area, of the head and of the body and tail of the pancreas are more conflicting. The diverse results reported by various authors probably depend on two factors: the methods used in making the diagnosis, and the type of material included in the study. Diagnoses made on purely clinical grounds are obviously subject to error, but incorrect conclusions may also be drawn after the pancreas is palpated at operation and a biopsy taken.[3] Accurate diagnosis is made possible only by autopsy or by operative procedures that resect large blocks of tissue. The experience of Ransom[15] is illustrative: of 10 patients examined at laparotomy, 6 were considered to have pancreatic carcinoma and 4 ampullary neoplasms, whereas autopsy revealed that only 3 of these patients had cancer of the pancreas; in 7 cases the primary site was the common bile duct.

Whether the diagnosis is made at operation or post mortem also affects the material included in an analysis of cases. Patients observed at operation contain a preponderance of cancers of the ampulla or of the head, for cases of this type present symptoms calling for operative intervention. Cattell,[3] for example, states that carcinoma of the ampulla is more frequent than that of the pancreas. A series based on material at autopsy, however, may reveal that lesions of the tail of the pancreas occur much oftener than one would suspect after analyzing surgical material.[16] Finally, the diffuse nature of many pancreatic cancers makes it merely a matter of individual opinion whether or not the primary lesion is placed in the head.[6] As a rough approximation, however, one may expect to see three cancers of the head of the pancreas for every one that involves the body and the tail. The relative frequencies of pancreatic and periampullary lesions are indicated by the following figures: cancers of the pancreas have been reported in 0.30 to 0.75 per cent of all autopsies,[6] whereas the incidence of periampullary carcinomas is said to range from 0.04 to 0.20 per cent[17, 18] of all post-mortem examinations.

For many years it has been the practice to separate cancers in the head of the pancreas from those in the tail on the basis of clinical and pathological differences. The wisdom of this practice has been challenged by Berk,[6] who emphasizes the difficulty of diagnosing and delineating pancreatic neoplasms, and who suggests that overemphasis of the single symptom of jaundice interferes with a broad conception of the symptoms and signs to be expected in all cases of pancreatic cancer. Another frequently quoted difference — that cancers in the ampulla or head grow slowly and metastasize late, whereas those in the body and tail grow and spread rapidly — may be more apparent than real. That this difference has been observed at autopsy or at operation is unquestioned. In 28 patients dying of ampullary carcinoma, Baggenstoss[18] found no evidence of metastases in 15; in the 16 cases of cancer of the body or tail reported by Duff,[16] metastases were present in all but 1. Perhaps an intrinsic difference between the two lesions exists, but the influence of other factors is excluded with difficulty. Lesions in the head of the pancreas usually obstruct the hepatic or pancreatic ducts, and the resultant chain of events leads either to surgery or to death on the basis of hepatic or pancreatic failure before the neoplasm has a chance to grow or spread. In cancers of the body and tail, however, no vital processes are disrupted by the primary growth, and the patient slowly dies of cachexia and inanition as the cancer invades and metastasizes. This rather obvious explanation of the apparent difference between cancer in the head and tail of the pancreas has, of course, been recognized by various writers but has been dismissed as a contributory factor on the basis of various theoretical arguments.[16, 19] That the dismissal is somewhat premature, however, is indicated by the observations of Orr,[20] who successfully removed periampullary carcinomas in 8 patients, 5 of whom subsequently died of metastases.

Heterotopic pancreatic tissue occurs in various portions of the digestive tract, but the duodenum, stomach and jejunum are the most frequent sites. Like other pancreatic tissue, these aberrant cells are subject to malignant degeneration[21] and may account for some of the cancers of the small bowel.[22]

The factors that make it difficult to collect accurate statistics on the pathology of pancreatic and ampullary cancers also introduce discrepancies into an analysis of the symptoms produced by these diseases. The incidence of jaundice may serve as illustration. Since this finding is the usual reason for surgery in patients with pancreatic neoplasm, its occurrence in surgical material is practically constant. Except in pancreaticoduodenectomy the surgical diagnosis of cancer of the pancreas depends on palpation of a nodule or mass in the head of the gland, metastases or an occasional biopsy attesting to the malignant nature of the process. In a series of surgical cases jaundice is consequently found to be the outstanding symptom of pancreatic carcinoma. A pathologist, however, might classify many of the nodules in the head of the pancreas as periampullary neoplasms. Deprived of these cases and increased by relatively nonicteric cases of pancreatic cancer, a series studied at autopsy reveals that jaundice is a frequent but far from invariable symptom of pancreatic cancer.

The marked effect that the diagnostic method may have on the observed incidence of a symptom and the variability of the methods from one series to another suggests that the true incidence of jaundice — or of any other symptom — cannot be derived merely by the process of averaging the incidences reported by all who have discussed cancer of the pancreas. Such averages are at best approximations, and the assignment of an exact figure carried to two decimal places to the incidence of any symptom of pancreatic cancer seems to impart an

unwarranted aura of accuracy. Nevertheless, three symptoms occur so frequently that there is no doubt concerning their prevalence. These symptoms are weight loss, pain and jaundice.

Weight loss, sometimes totaling as much as 50 pounds, is almost invariably evident; only a rare case report states that the patient had lost no weight when first seen.[23, 24] One may question whether this loss, particularly one of 20 pounds or more, does not indicate advanced disease and preclude operability. In some cases weight loss carries such an implication, especially if the neoplasm arises in the body or tail of the pancreas. In others, however, weight loss occurs because a small periampullary neoplasm obstructs the flow of digestive juices. In lesions of this type weight loss certainly does not contraindicate operation, as is evident from Cattell's[3] figures. Of 18 patients who were subjected to pancreatic resection, 16 had experienced preoperative weight loss, 13 had ampullary lesions and 13 enjoyed what appeared to be a successful result. When weight loss is the manifestation of a carcinoma in the head of the pancreas, its significance is variable: it may mean that the growth is inoperable, but it may also be the result of an associated diabetes, of a widespread destruction of the acinar elements or of secondary gastrointestinal disorders, such as nausea and diarrhea. A patient whose case was recently reported, for example, had lost 50 pounds because of an extensive pancreatic cancer; yet a total pancreatectomy was feasible, and the patient appeared to be doing well a year after operation.[25] One must conclude that progressive weight loss is an important symptom not only of all pancreatic cancers but also of those susceptible to operative removal.

Pain ranks as the second most significant symptom of cancer of the pancreas. The association of painless jaundice with pancreatic carcinoma seems to be so firmly rooted in the medical mind that almost every recent writer on this subject has felt it necessary to emphasize repeatedly that at least three fourths of the patients with cancer of the pancreas do have pain. Ampullary cancers are said to occasion less pain and are held responsible for many cases of painless jaundice,[3, 9, 26] but in one series more than half the patients studied complained of pain.[10] The character of the pain in pancreatic or ampullary cancer is extremely variable and can be misleading in that it may mimic biliary or intestinal colic. In many cases, however, its features are almost specific: it is dull, boring and often severe. It is located in the upper abdomen, either on the right or on the left, and radiates through to the back.[27, 28] It is not related to eating, bowel movements or physical activity, but is often aggravated when the patient lies on his back. In such cases the patient usually complains that the pain is worse at night, and the attending physician may find "a nervous, apprehensive patient sitting up in bed, bending forward over folded arms which rest against his epigastrium, and maintaining his position hour after hour because it gave the most relief from pain. . . ."[24] Cases of this type should be suspected of being cancer of the pancreas and should not be classified as psychoneurosis or back strain.

Careful pathological examination indicates that neoplastic invasion of nerves occurs in many cases of pancreatic carcinoma.[29] In addition to the deep somatic nerves, the celiac plexus of sympathetic nerves is presumably most subject to invasion by reason of its position adjacent to the pancreas. Since both the somatic and sympathetic nerves can transmit pain impulses, it is possible that back pain in pancreatic cancer is produced in part by neural invasion. Actually, a fair but not a perfect correlation between back pain and invasion of the nerves has been found.[29]

Whether or not jaundice occurs as an early symptom depends, of course, on the site of the lesion. Thus the fact that obstructive jaundice develops early in about two thirds of the cases merely expresses the relative incidence of lesions in or near the terminal portion of the common duct. Late in the course of pancreatic cancer, jaundice becomes a frequent symptom, even when the primary lesion originates in the body or the tail, but jaundice in these cases merely indicates that the disease is advanced, with extensive metastases to the liver and to the lymph nodes surrounding the extrahepatic bile ducts.

The jaundice that occurs early is usually steadily progressive and obstructive. It is not an invariable concomitant of cancer of the head of the pancreas, however, nor is it always of a steadily progressive character.[9] Ampullary cancers in particular may produce an inconstant icterus, for these lesions, which are situated near the orifice of the common duct, are subject to necrosis and sloughing and thereby allow an intermittent flow of bile.[14] In a series of 40 cases of ampullary carcinoma, jaundice was fluctuating in 32 and intermittent in 8.[10]

Since jaundice occurs early in only 2 out of 3 cases of pancreatic cancer and since only 1 out of 4 patients is free from pain, it follows that painless jaundice is not a frequent characteristic of cancer of the pancreas; Berk[6] estimates its incidence at about 20 per cent. When it does occur, it presents a symptom complex that is significant for the diagnosis of pancreatic or ampullary cancer. Perhaps because of this fact, it continues to be stressed in the literature in a way that is completely out of proportion to its incidence. In one report, for example, "painless obstructive jaundice, with diminished or absent ferments," is considered to favor the diagnosis of carcinoma of the pancreas, but the case summaries reveal that of 12 patients with cancer of the pancreas studied, 8 complained of pain.[30]

In addition to weight loss, pain and jaundice, pancreatic cancer may give rise to a number of other

symptoms and signs, many of which, such as anorexia, weakness, edema and fever,[13, 31] are nonspecific and do not help in reaching a diagnosis. Gastrointestinal symptoms of all types are of course prevalent, one of the most frequent being a change of bowel habits. Constipation predominates over diarrhea. It has been suggested that a normal red-cell count and the absence of occult blood in the stools of a patient who otherwise presents symptoms suggesting upper gastrointestinal cancer should make one suspicious of pancreatic neoplasm.[6] Although this is true of many patients, others may vomit blood or may exhibit melena for one of the following reasons: the pancreatic cancer may have eroded into the stomach or duodenum; esophageal varices may have formed secondary to neoplastic invasion and thrombosis of the splenic or portal vein; hypoprothrombinemia may exist because of obstructive jaundice; and a primary lesion at the ampulla may have become ulcerated. Ulceration of ampullary carcinoma was described in 57 of 222 cases collected by Lieber, Stewart and Lund,[14] and in 40 cases analyzed by Sharpe and Comfort,[10] 25 patients had either tarry stools or stools containing occult blood.

"I have several times, in the wards, — pointed out to you that obliterative phlebitis is not a symptom which belongs peculiarly to cancer of the stomach, but that it is equally symptomatic of cancer of any other internal organ." These words of Trousseau[32] were echoed about seventy years later by Sproul,[33] whose analysis of material at autopsy indicated that between 15 and 25 per cent of patients with most varieties of abdominal cancer suffer from venous thrombosis in the abdomen or legs. In 16 cases of cancer of the body or tail of the pancreas, however, venous thromboses were found in 9 — more than twice the incidence of such thromboses with gastric cancers or with cancers in the head of the pancreas. In some cases the tendency toward thrombosis was apparently so pronounced that nonbacterial vegetations formed on the heart valves, a phenomenon that was subsequently observed in another typical case of cancer of the pancreatic tail and body.[34] Sproul and later Kenney,[19] impressed by the frequent association of venous thromboses and neoplasms in the tail and body of the pancreas, concluded that these growths per se must affect the clotting mechanisms of the blood. As yet, this hypothesis has not been proved, nor has the progressive but relatively prolonged cachexia typical of cancers in the tail and body been ruled out.[35] Furthermore, the increased incidence of thrombosis in cancers of the body and tail of the pancreas as compared with that in those of the head may also indicate that lesions in the head produce a decreased clotting tendency, a possibility that must be considered in view of the hypoprothrombinemia that attends obstructive jaundice.

In these days of marked emphasis on psychosomatic disorders, it is well to point out that nonicteric patients with pancreatic carcinoma are almost invariably suspected of having a marked psychoneurosis, partly because of the negative results obtained after the physician has exhausted his usual diagnostic armamentarium. But the situation is often more complex, for Yaskin[36] and subsequently others [24, 37] reported cases of pancreatic cancer in which competent psychiatrists made diagnoses of advanced states of anxiety or depression. The association of pancreatic cancers, especially those of the body and tail, with psychiatric abnormalities does not establish a causal relation, but it does carry a warning: progressive anorexia, weight loss and back pain suggest cancer of the pancreas, regardless of whether the patient has psychiatric manifestations at the same time.

The physical signs of pancreatic cancer are manifold and depend on the location, size and spread of the tumor. A palpable mass may be discovered on rare occasions before the cancer has spread, but this finding usually indicates inoperability as much as do a rectal shelf, ascites, abdominal varices and obvious metastases to the liver, lungs or lymph nodes. A sign that may occur early and to which much interest pertains is a palpable gall bladder in patients who exhibit obstructive jaundice. This sign, of course, is linked with the name of Courvoisier, whose law, as translated literally by Ransom,[15] is as follows:

> With obstruction of the common duct by stone, dilatation of the gall-bladder is rare; the organ is usually shrunken. With obstruction of other kinds, on the contrary, distention is the rule; shrinking occurs in only one twelfth of these cases.

Opinions regarding the reliability of Courvoisier's law differ widely in that palpable gall bladders have been noted by some authors[8, 9] in less than 10 per cent of jaundiced patients with cancers in the ampulla or pancreatic head. Others, however, have palpated a distended gall bladder in 62 per cent of these cases. Reviews of the literature indicate that on the whole a distended gall bladder can be detected clinically in about half the cases of pancreatic cancer with jaundice,[6, 14] but that at autopsy or operation enlarged and tense organs are found in about four fifths of the cases.[6, 10, 15] The discovery of a large, relatively nontender gall bladder in a patient with obstructive jaundice may therefore be regarded as evidence for a neoplastic obstruction of the extrahepatic biliary passages, but a negative finding — that is, failure to palpate the gall bladder — is of little help in ruling out this diagnosis. A not inconsiderable number of patients have both gallstones and pancreatic cancer, a combination that makes the diagnosis extremely difficult.[14]

The following laboratory tests are significant in the diagnosis of pancreatic carcinoma: stool exami-

nation for excess fat and protein, determination of glucose in blood and urine, analysis of serum and duodenal contents for pancreatic enzymes and, if jaundice is present, the establishment of its obstructive character.

As has been known for many years, a diffuse carcinoma involving the whole pancreas or a small lesion so situated as to block the pancreatic ducts may impair the digestion of fat and proteins, which consequently appear to excess in the feces. The stools are then light colored, greasy and bulky, the weight of the stools occasionally reaching five times normal.[38] In spite of the fact that steatorrhea and creatorrhea are well established findings in cancers of the pancreas, little information exists regarding the frequency of their occurrence. After reviewing the literature, Berk[6] concluded that less than 10 per cent of patients with pancreatic cancer pass fatty stools. One must remember, however, that most series of cases are taken from hospital files, are rarely studied by the author himself, are often not suspected of having pancreatic cancer during life, and that "rarely, even in leading hospital clinics, are the stools adequately examined."[38] On the other hand, steatorrhea and creatorrhea occur rather late in the course of pancreatic disease,[39] and some patients may have fairly normal stools, even after complete pancreatic atrophy[40] or resection.[41] A rough estimate indicates that a fourth of the patients with ampullary or pancreatic carcinoma pass fatty stools with a high nitrogen content, but that unless the patient is jaundiced — that is, obstruction is present in the ampullary area — steatorrhea and creatorrhea indicate advanced disease.

Precise analyses of stools are troublesome to carry out, not the least difficulty being a quantitative three-day stool collection, but if facilities are available, quantitative analyses for fat and nitrogen are of great help. Normal persons usually excrete less than 5 per cent of the fat intake and rarely pass more than 12 gm. of fat in the stools a day.[42] In pancreatic steatorrhea 30 to 50 per cent of the intake may be lost in the stools. (It should be noted that excretions of fecal fat expressed in absolute values, such as grams per day and percentage of intake, are significant; fecal fat expressed as percentage of dry weight of the stool gives a rough index but is not completely satisfactory, since the percentage of fat varies inversely with the amount of other material in the dried stool.)

Although facilities for quantitative measurement of the daily fecal fat loss may not be available, there is little excuse for not staining a stool sample with an alcoholic solution of sudan III. This stain imparts a red or orange color to fat droplets and to some crystalline and amorphous lipid material, although the orange-staining fatty-acid crystals frequently described in laboratory manuals are rarely seen. A careful study by Andersen[43] showed that the amount of sudan-staining material is an excellent indication of the percentage of fat present in the stool but only a fair indication of the total fecal fat. She concludes that a negative finding (less than 2 fat droplets per low-power field) and a ++++ finding (about half the visible material stained with sudan) are highly significant. When mineral oil is used, the test is unreliable. Another important contribution made by Andersen are her observations suggesting that bacteria in the colon split neutral fats. This explains why patients with pancreatic deficiency excrete so much split fat in the stools, when one would expect the deficiency in lipase to result in a large output of unsplit, neutral fat.

Pratt[38] believes that pancreatic deficiency in protein digestion can be detected by the identification of meat fibers on microscopic examination of the stool. Other investigators[44] consider the presence of meat fibers less significant, since they may be found in other forms of diarrhea and since the digestion of meat is related to gastric as well as pancreatic function. The question is important, for the amount of nitrogenous material excreted in the feces provides a good means of separating pancreatogenous steatorrhea from that of sprue or pure biliary obstruction.[42] In normal persons and in patients with nonpancreatogenous steatorrhea, the daily fecal nitrogen excretion is less than 3.0 gm.; in patients with pancreatic deficiency the creatorrhea exceeds this amount.[45]

Cancer of the pancreas and abnormalities in carbohydrate metabolism occur together more frequently than can be accounted for on the basis of chance. The reported figures on the coincidence of these diseases vary widely, but again the differences may depend on the criteria used in diagnosing diabetes,— glycosuria, an elevated fasting blood sugar or an impaired glucose-tolerance curve. Using the glucose-tolerance test, Berk[6] found abnormal results in 7 out of 9 cases, but an elevated curve was found in only a fifth of the cases he collected from the literature. This ratio corresponds to the average incidence of glycosuria and fasting hyperglycemia reported by various subsequent writers, but the individual figures vary from zero[9] to 30 per cent.[7] The situation is analogous to that pertaining to fatty stools: evidence for diabetes increases in proportion to the effort made to uncover abnormalities of sugar metabolism.

At first glance, the association of pancreatic carcinoma and a diabetic condition seems obvious. Actually the situation is more complex. Even with extensive neoplastic replacement of acinar tissue, the islands of Langerhans may be spared.[46, 47] So far as can be judged from the pathologic picture, consequently, many cancers of the pancreas are not diffuse enough to account for an associated diabetes. Furthermore, in many cases, the diabetes antedates the symptoms of pancreatic cancer by many years.[47, 48] In keeping with this fact, Marble[47] found

that in 256 patients who suffered from both diabetes and cancer, pancreatic cancer, which was definitely proved in 21, accounted for 8 per cent of all carcinomas in the diabetic cases as compared with 1 or 2 per cent in the population at large. These figures suggest the possibility that diabetes is occasionally the precursor of cancer of the pancreas, rather than vice versa. Although a definite causal relation between diabetes and pancreatic cancer cannot be established, the two conditions coexist frequently enough for any suggestion of a diabetic state to intensify suspicion of pancreatic cancer if the clinical picture is otherwise suggestive.

With the development of methods for determining the concentrations of pancreatic enzymes in the blood and the duodenal contents, it was hoped that the diagnosis of pancreatic disease would be greatly facilitated. This hope has been realized only in part, for results well within the normal range may be obtained unless the cancer obstructs the pancreatic ducts or destroys more than half the pancreatic acini. Another, somewhat different, source of difficulty is the great number of methods and modifications of methods used by various investigators. Some standard methods of determining and some standard units of expressing concentrations of pancreatic enzymes must be adopted before the value of this analysis can be appraised.

Determination of the serum amylase (diastase) concentration has occasionally yielded a high figure in cases of pancreatic cancer, but on the whole not much help can be expected from this test.[44, 49] The urine amylase content, which fluctuates more than the serum content, is even less significant.[38, 48] Determination of serum lipase, by contrast, is of the greatest value. In the Cherry–Crandall[50] method, which is almost universally used, the lipase content of the serum is expressed as the number of cubic centimeters of 1/20 normal sodium hydroxide solution necessary to neutralize the fatty acids formed by the action of 1 cc. of serum on an olive-oil substrate. Johnson and Bockus,[51] who placed the upper limit of normal for this test at 1.0 cc., found an elevated lipase in 16 out of 30 cases of pancreatic cancer "at least once during the course of the illness." Even if 1.5 cc. is used as the upper limit of normal, an elevated serum lipase is found in about half the cases of pancreatic cancer.[49, 52] Similar results can be expected in patients with tumors of the ampulla.[52] As has been emphasized, an elevated serum lipase or amylase implies pancreatic disease,[52] but not the type; a clear-cut dissociation, however, with a persistently high lipase and a normal amylase, suggests cancer.[49] Some cases of an obstructing ampullary lesion with initially elevated values for serum lipase may eventually display values in the low normal range, since the obstructed acinar cells atrophy or are invaded by neoplasm. A cancer of the pancreatic acini with function is rare, but such a case has apparently been observed,[53] since the concentrations of the serum amylase and lipase were, respectively, nearly one hundred times and ten times the normal values.

On the basis of experiments performed with dogs, Popper and his associates[54, 55] suggested that valuable information could be obtained from serum enzyme determinations after stimulation with an intravenous injection of secretin and a subcutaneous dose of acetyl-beta-methylcholine chloride (Mecholyl). If this stimulation fails to elevate the serum concentrations of amylase and lipase, the authors believe, pancreatic hypofunction may be suspected. On the other hand, elevation of the serum lipase after an intravenous injection of secretin insufficient to alter the level in a normal subject suggests obstruction of the pancreatic ducts.

The pancreatic secretion in cases of pancreatic cancer may be reduced in volume and may contain a decreased concentration of bicarbonate, amylase, trypsin and lipase. The reductions are often noticeable in the fasting secretions, but the deviation from normal is more apparent if the pancreas is stimulated with secretin or acetyl-beta-methylcholine chloride. The former has been relatively unavailable, but the results obtained with the latter should be equally if not more satisfactory, since the drug stimulates a secretion of normal volume but of increased enzyme concentration,[56] and it is stated that the enzyme output is the first to suffer in pancreatic disease.[57] Over half the cases of pancreatic cancer are reported to exhibit a decreased enzyme concentration in the duodenal juices (Table 1). Possibly a somewhat false impression of the value of the test in the early diagnosis of pancreatic cancer is given by the data, for cases with advanced disease are included. Nevertheless, analysis of the duodenal

TABLE 1. *Data in 37 Cases of Pancreatic Cancer Reported in the Literature.*

AUTHOR	TOTAL NO. OF CASES	SITE OF CANCER	REDUCTION IN VOLUME AND BICARBONATE SECRETION	REDUCTION IN TOTAL ENZYME OUTPUT	ICTERUS
Agren and Lagerlöf[58]	7	Head, 6 Body, 1	3	4	4
Bauman and Whipple[30]	11	Head, 9 Not stated, 2	Not stated	10	7
Pollard, Miller and Brewer[59]	6	Head, 5 Tail, 1	3	3	Not stated
Friedenwald and Morrison[11]	8	Not stated	Not stated	5	Not stated
Diamond and Siegel[60]	3	Head, 3	2	3	3
Pratt, Brugsch and Rostler[61]	2	Head, 2	2	2	2

contents for pancreatic ferments after stimulation with secretin or acetyl-beta-methylcholine chloride yields invaluable information, particularly since depression of pancreatic enzymes may precede the onset of jaundice or steatorrhea.[39, 58, 62]

Scattered case reports indicate that the sedimentation rate is elevated in advanced cases of cancer of the pancreas, but this test usually gives normal results when the lesion is small and localized.[39, 58]

When a patient is icteric, it is the function of laboratory tests to determine the type and course of the jaundice. Jaundice that results from pancreatic or ampullary cancer is typically progressive, nonfluctuating and obstructive — that is, the stools remain acholic, the heavily bile-stained urine contains no urobilinogen and almost all the serum bilirubin can be quantitated with the direct van den Bergh reaction. The completeness of the obstruction produced by the usual neoplastic invasion or compression of the external biliary passages is reflected in the fecal urobilinogen content. Measured by Watson's[63] method, the daily fecal output of urobilinogen in patients with obstructive jaundice caused by carcinoma is less than 5 mg.; in those with noncancerous jaundice of the obstructive type — caused by common-duct stones, strictures, pancreatitis or severe hepatitis — the urobilinogen output in the stools is greater. Although this test is helpful in the diagnosis of many pancreatic or ampullary cancers,[64] the results may be misleading in cases of ampullary tumors that exhibit fluctuating or even intermittent jaundice.

Since there is no method of direct x-ray study of the pancreas, the roentgenographic demonstration of tumors in this organ depends on abnormalities produced in its adjoining hollow viscera. A small intrapancreatic or a diffuse scirrhous cancer that replaces the normal tissue without concomitant enlargement of the gland may consequently go undetected in spite of painstaking radiologic examination. Large tumors may displace the stomach upward and ventrally, the descending duodenum laterally and the transverse duodenum and transverse colon downward.[26, 65] Of these deformities, a large C-shaped duodenal loop is perhaps the best known, but its interpretation is often difficult, especially in hypersthenic persons. In patients of this habitus, the stomach is usually stretched across the spine high in the epigastrium and thus exposes the whole duodenal loop, which has an appearance of enlargement.

Massive displacement of the adjoining viscera by a pancreatic cancer is a poor prognostic sign, since it suggests a large and advanced neoplasm. Smaller cancers situated in the periphery of the pancreas may, however, manifest themselves by the production of localized deformities in the gastrointestinal tract. Changes in the mucosal pattern or alterations in the finer outlines of the stomach or duodenum may appear before the cancer has invaded the mucosa; later filling defects and evidence of ulceration may develop as the tumor extends into the lumen of the bowel. So far as the duodenum is concerned, considerable attention has been directed to the so-called "reverse figure-3" sign. As originally described by Frostberg,[66] the entire descending duodenum participates in forming such a sign, the top of the figure starting just beyond the duodenal cap, its lower pole at the beginning of the transverse duodenum and the prong in the middle of the figure pointing toward the spine in the region of the ampulla. Frostberg, who found this duodenal configuration in 1 case each of pancreatitis, of cancer of the pancreas and of cancer of the ampulla, assumed that it was produced by pressure on the medial wall of the duodenum, with relative fixation of the ampullary area. Other authors[67–69] have used the reverse figure-3 sign to describe smaller lesions that at times seem to include only the lips of the papilla of Vater, the central prong of the figure being formed by the entrance of the ampulla. Both large and small configurations are sometimes observed in normal duodenums.[26, 66]

When case records of patients with pancreatic or ampullary cancer are reviewed, the incidence of gastrointestinal abnormalities as demonstrated by x-ray examination varies markedly in different series. In some, positive findings are claimed in nearly three fourths of the cases[17, 47]; others report an incidence of about 50 per cent,[6, 7] whereas still others[8, 10, 15] consider abnormal roentgenologic findings unusual. Although some abnormality in the radiologic appearance of the stomach, duodenum or colon may be observed in about a third of the cases of pancreatic or ampullary cancers, the findings are diagnostic in a much smaller number, especially if indications of an early lesion are being sought.

A rather ingenious method of visualizing the pancreas was proposed by Engel and Lysholm[70] twelve years ago. This consisted of having the patient lie prone, inflating the stomach with air through a tube or by giving an effervescent mixture and then taking a lateral roentgenogram. Ideally the gas in the stomach tends to outline the dorsal aspect of this organ, and the pancreas appears as a shadow between the air-filled stomach and the lumbar vertebras. Using this technic, Engel and Lysholm[70] and Holm[71] believed that they had obtained positive results in 86 per cent of their cases of pancreatic cancer. Enlargement of the pancreas, however, must be present if positive results are to be obtained by this method, and false-positive reactions may occur in short, thickset persons who have excess retroperitoneal fat.[70, 72]

In patients who have a tube in the common duct after choledochostomy, cholangiography occasionally reveals the presence of a pancreatic cancer by demonstrating a dilated common duct that is cut off rather abruptly at its distal end.[73, 74] If the

head of the pancreas is free of disease, pancreatic reflux sometimes complicates cholangiography, but apparently no tumors of the body or tail have been discovered by this method.[76] Peroral catheterization of the ampulla of Vater has been tried in cadavers, but must be difficult in patients living.[76] A method that may hold some hope for the early identification of lesions in the pancreatic head or the ampulla is the nonsurgical cholangiography developed by Royer and Solari.[77] By this method, the gall bladder and bile ducts are injected with radiopaque material through a peritoneoscope. Demonstration of an enlarged gall bladder, of dilated biliary passages and of the obstructed end of the common duct is perhaps feasible by this technic in patients suffering from pancreatic or ampullary cancer.

Summary

Improved surgical methods of removing tumors of the pancreas or ampulla of Vater demand early diagnosis of these diseases. In many cases this goal cannot be achieved with present knowledge and technic. In others, the fatal delay that withholds a possible surgical cure from the patient can be avoided by an appreciation of the following facts.

Almost all patients with cancer of the pancreas lose weight rapidly and progressively. Many of them have a boring upper abdominal and back pain unrelated to any gastrointestinal function. Many others have obstructive jaundice. The combination of any two of these symptoms is highly indicative of pancreatic cancer, particularly if the patient is a man over forty years of age.

A palpable, nontender gall bladder in a jaundiced patient is suggestive of cancer in or near the head of the pancreas. The absence of this sign does not exclude pancreatic cancer.

Laboratory tests, as a rule, are helpful when positive and of little significance when negative. Particularly suggestive are the following: a persistent obstructive jaundice, with acholic stools and no urobilinogen in the urine; a high serum lipase and a normal serum amylase; absent or greatly diminished enzymes in the pancreatic secretion stimulated by secretin or acetyl-beta-methylcholine chloride; and stools containing an excess of both fat and nitrogen.

Less significant, but consistent with the diagnosis of pancreatic cancer, are hyperglycemia, glycosuria or impaired glucose tolerance and an elevated sedimentation rate.

At present, the roentgenologic diagnosis of pancreatic cancer depends principally on deformities produced in adjoining hollow viscera. Greater use of new technics may increase the usefulness of the x-ray in the diagnosis.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 32441

PRESENTATION OF CASE

A forty-nine-year-old salesman entered the hospital because of severe dyspnea.

At approximately twenty years of age, the patient developed a chancre for which he received intravenous injections of an "antisyphilitic drug" over the course of a year. He was well until three years before admission, when a left Bell's palsy occurred a day following exposure to cold air while he was sleeping outdoors. At about the same time he began to experience shooting pains in the lower back and at times down the legs and arms. Two months before admission he was awakened by a severe precordial pain radiating to the left shoulder. He sweated, felt suffocated and feared impending death. Partial relief was obtained from an injection given by a physician. The patient coughed blood-streaked sputum for four days. There had been no previous cardiac or pulmonary symptoms, although the patient was known to have a systolic blood pressure of 170. At the end of four days he entered the Emergency Ward, where a Grade II apical systolic and a questionable aortic diastolic murmur were heard. There was no tenderness over the leg vessels. The pupils were fixed, the left one being oval in a perpendicular plane. An x-ray film of the chest was negative except for calcification of the aorta. The cardiac consultant described faint systolic and early, blowing diastolic murmurs at the aortic areas, as well as a presystolic murmur at the apex. An electrocardiogram showed inverted T_1T_{CF4} and T_{CF5}, and upright T_2 and T_{CF2}. Left-axis deviation was present, with a PR interval of 0.14 second. The blood Hinton reaction was positive, the blood Wassermann reaction was negative, and the spinal-fluid Hinton and Wassermann tests were positive; the gold-sol curve was 4442210000. The precordial pain cleared spontaneously, and the patient was discharged on the fourth day to the Out Patient Department, where he was given four 0.2-gm. intramuscular doses of bismuth at weekly intervals for a month. The facial palsy appeared worse at the end of this time, and severe attacks of nocturnal dyspnea and nonradiating precordial oppression suddenly began. Later the patient became dyspneic and orthopneic during the day. A week before admission, after three weeks of severe dyspnea, the voice became hoarse.

On examination the patient was orthopneic and hoarse. There was a blowing, Grade III diastolic murmur in the aortic area and down the left sternal border and a Grade II diastolic mitral murmur. There were dullness, decreased breath sounds and sticky rales at both bases, more on the left than on

the right. The liver edge extended 5 cm. below the costal margin. There was slight pitting edema of the ankles. The pupils were fixed to light but reacted to accommodation. A facial paralysis was present.

The temperature was 100°F., the pulse 100, and the respirations 21. The blood pressure was 125 systolic, 25 diastolic.

Examination of the blood showed a red-cell count of 5,170,000, with 12.9 gm. of hemoglobin per 100 cc., and a white-cell count of 10,400, with a normal differential. The urine was normal.

In the hospital the patient was restless and dyspneic and complained of substernal burning. On the morning after admission he became extremely restless and then manic; he clutched wildly at his chest, complained of precordial pain and died in a few minutes.

Differential Diagnosis

Dr. Edward F. Bland: The first and foremost feature of this case is syphilis. The initial infection began twenty-nine years before the final disintegration. The early treatment was inadequate by present standards, and in due course the patient appears to have developed active neurosyphilis and almost certainly fatal cardiovascular syphilis. The first clinical feature of some interest is centered around the possibility of neurosyphilis. In addition to the positive serologic findings and abnormal gold-sol curve, he had typical Argyll–Robertson pupils. Furthermore, the spinal-fluid Wassermann reaction was positive. In this connection, one would like to know the spinal-fluid cell count and the protein content, as well as the state of the peripheral reflexes.

Dr. Tracy B. Mallory: The total protein was 24 mg. per 100 cc. There is no record of the cell count.

Dr. Bland: That does not help much. I expected that it might be elevated. Nevertheless, in view of the shooting pain three years before entry and the abnormal findings in the spinal fluid, I suspect that the patient had active late neurosyphilis.

How are we to interpret the seventh-nerve palsy? Isolated seventh-nerve palsy is rarely due to syphilis. In this case I attribute it to peripheral neuritis following exposure to cold.

Then, we come to his admission to the Emergency Ward, which followed the sudden onset of precordial pain that radiated to the left shoulder for four days, and the raising of bloody sputum. We do not know whether there was fever, what was heard in the lungs, or whether breathing was painful. We are told simply that the patient had pain, which was presumably imperfectly relieved by morphine. What could this have been? A pulmonary infarct, of course, is the first thing that comes to mind. The radiation of the pain is consistent, but it would be helpful to know some of the other clinical details mentioned above.

To what else could it have been due? A coronary occlusion? The electrocardiogram is consistent with that diagnosis. It could also have been due to uncomplicated acute pulmonary congestion from left ventricular failure, or to congestion behind a marked mitral stenosis. It could also have been due to an infection or an expanding (or leaking) aneurysm. I favor pulmonary infarction as the most probable explanation for this illness. Furthermore, I should like to know what the blood pressure was at that time, in view of the abnormal blood-pressure determination recorded a month later. The electrocardiogram was definitely abnormal.

Dr. Mallory: The blood pressure was 120 systolic, 20 diastolic.

Dr. Bland: That is a wide pulse pressure and not significantly different from that on the second admission. Therefore, the patient had free aortic regurgitation in spite of the uncertainty about the murmurs. This illness with pain and hemoptysis must not have been taken too seriously, because he remained only four days in the hospital.

Then we come to the physical signs, which were largely limited to the heart. He had a wide pulse pressure, and one observer thought that he had aortic regurgitation. In addition, the characteristic murmur of mitral stenosis was described. That can be present in the absence of mitral stenosis if there is marked dilatation of the heart secondary to free aortic regurgitation. As the murmur is described, however, one must seriously consider the possibility of rheumatic mitral-valve involvement. The electrocardiogram was abnormal but not diagnostic and not particularly suggestive of a recent myocardial infarct. The abnormal findings could have been due to left ventricular strain in the presence of the wide pulse pressure and the evidence of aortic regurgitation. This explanation seems most probable, with perhaps the added effect of constricted coronary ostia. There was not a later tracing by any chance?

Dr. Mallory: No. Since the first admission was simply to the Emergency Ward, there was no complete workup.

Dr. Bland: The patient did fairly well. He went home and had four injections of bismuth. Thereafter he rapidly became worse and in the course of a month returned in a serious state, with acute and rapidly progressive heart failure. Until I knew what the blood pressure was at the first admission, — it was not referred to in the original record, — I was inclined to put some emphasis on the apparently striking increase in the aortic regurgitation within a month. The question is, Did the treatment do him any harm? He had had no penicillin. He had had no arsenic. These are the two drugs whose administration might seriously be questioned in the

presence of advanced cardiovascular syphilis with heart failure. Bismuth does not ordinarily cause a Herxheimer reaction by rapid resolution of syphilitic inflammatory tissue. It can cause slow resolution of a gumma, but we have no reason to think that this man had gummatous lesions. At this point one would like to examine the x-ray films.

DR. JAMES R. LINGLEY: I am sorry. The x-ray films have been destroyed.

DR. BLAND: I should have liked to know whether the calcification was limited to the first portion of the aorta. The roentgenologists repeatedly call our attention to the fact that this finding is an important clue to the presence of syphilitic aortitis. Is that correct, Dr. Lingley?

DR. LINGLEY: Yes.

DR. BLAND: I should also have liked to know the size of the aorta and of the heart. Presumably, both were dilated. The terminal rapid disintegration and heart failure is further evidence consistent with cardiovascular syphilis. Therefore, I cannot seriously consider any other diagnosis. I could discuss at length the various details of what may have happened at the end. I shall conclude, however, that the patient had neurosyphilis, which was late and possibly active, and that he had cardiovascular syphilis, aortitis and free aortic regurgitation. It is likely that the coronary ostia were constricted by the syphilitic process. I am bothered by the apical diastolic murmur, which, as described in the record, is characteristic of mitral stenosis. The patient died primarily of congestive heart failure.

CLINICAL DIAGNOSES

Syphilitic aortitis.
Aortic regurgitation.
Myocardial infarction.

DR. BLAND'S DIAGNOSES

Cardiovascular syphilis, with aortitis and aortic regurgitation.
Congestive heart failure.
Neurosyphilis, late, active.
Mitral stenosis?

ANATOMICAL DIAGNOSES

Syphilitic aortitis, with aortic insufficiency.
Cardiac hypertrophy and dilatation, predominantly of left side.
Infarct of heart.
Pulmonary edema, massive.
Hydrothorax.
Pulmonary tuberculosis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The autopsy on this man showed characteristic syphilitic heart disease. The valvular involvement was limited to the aorta. The cusps were separated at the commissures for a distance of 3 or 4 mm. The individual cusps were thickened, sclerosed and contracted. The aorta was markedly sclerotic, diffusely dilated, wrinkled and scarred in spots between the atheromatous plaques. The entire process was most marked in the thoracic portion of the aorta, diminishing as one proceeded toward the abdominal portion, which is characteristic of syphilis and in contrast to ordinary arteriosclerosis. The coronary ostia, especially that of the left coronary artery, were definitely narrowed by the aortic process. Beyond their mouths they were relatively free from atheroma; nevertheless, there was a large area of scarring at the base of the left ventricle, where the muscle was thinned to a width of only 3 mm. The gross appearance was quite consistent with an ordinary cardiac infarct. There was nothing in the microscopic sections to make one change that diagnosis — nothing, for instance, to suggest a gumma of the myocardium, which is occasionally seen. The lungs showed extensive tuberculous scars at both apexes surrounded by focal emphysema, a marked grade of chronic passive congestion and acute terminal pulmonary edema. They weighed over 2200 gm. at the time of autopsy and exuded turbid fluid on the slightest pressure. I cannot give the answer about the central-nervous-system involvement. We did not have permission to examine the brain, and the small section of the cord that was removed by the anterior approach did not show anything. I do not believe that that rules out the possibility of tabes.

CASE 32442

PRESENTATION OF CASE

A fifty-six-year-old woman entered the hospital because of a lump under the left breast.

The patient was apparently well until two years before entry, when she first noticed a small nontender swelling on the chest wall below the lateral portion of the left breast. This swelling increased slowly at first but more rapidly during the following year. It was never painful or inflamed, but several weeks before entry, the patient began to have occasional twinges of pain posterior to the mass.

The patient had had the usual diseases of childhood. Fifteen years before entry she had had typhoid fever, which cleared after four weeks without complications. Four years before entry the urine was reported to contain albumin. Three and a half years before entry she passed about 25 cc. of bright-red blood by rectum; a similar episode occurred two weeks before entry. A year before entry she had an attack of bronchitis requiring bed rest for a week. Six months later, the patient noticed slight exertional dyspnea and occasional episodes of tachycardia, but there was no orthopnea, ankle edema, cough or chest pain. During this period she also had frequency and nocturia (five or six times). There had been no recent weight loss.

The patient's mother, sister and brother had died of tuberculosis, and the patient had attended her brother during his final illness twenty years before entry.

Physical examination showed an obese woman in no distress. Over the chest wall anteriorly beneath the left breast, a hard, rounded mass measuring 4 by 6 cm. was firmly attached to the eighth and ninth ribs and moved with them. It had no connection with the breast. Firm pressure over the mass caused a "drawing sensation," with a slight ache radiating back along the ribs. The breasts were normal. The lungs were clear. The heart was normal except for a Grade I systolic murmur at the apex.

The temperature, pulse and respirations were normal. The blood pressure was 210 systolic, 110 diastolic.

The white-cell count was 5500, and the hemoglobin 12.5 gm. The total protein was 7.5 gm., and the fasting blood sugar 84 mg. per 100 cc. A blood Hinton test was positive. Examination of the urine was negative.

An x-ray film of the chest showed a 6-cm. soft-tissue mass overlying the anterior extremity of the left eighth rib. There was some bone destruction and thickening of the periosteum along the inner margin. The lungs were clear. An electrocardiogram was consistent with coronary disease.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Richard H. Wallace: It is unusual in a case of this sort — a tumor of the chest wall — to have so many hints in the history that might lead to a diagnosis.

I believe that the hypertension and heart disease had nothing to do with the mass in the chest wall. The patient had typhoid fever fifteen years before admission. It is possible, many years after typhoid fever, to have a rib infection from the typhoid bacillus, although a lesion of that sort is apt to be tender and is not likely to cause a tumor of this size and consistence. The second point is that on two occasions blood was passed by rectum, suggesting that three years previously the patient had had a primary cancer of the intestinal tract. But there is no further mention of the passage of blood, and no rectal examination, proctoscopic examination or barium study was done, so that the incident was presumably considered irrelevant.

The patient had had bronchitis and had certainly been exposed to tuberculosis, since her mother, brother and sister had died of it, and it is stated that she had taken care of her brother in his final illness, so that tuberculosis should be considered.

The statement that the blood Hinton reaction was positive immediately makes one think of gumma, which is not rare in the chest wall. It usually occurs, however, along the border of the sternum. Perhaps the x-ray films will be helpful.

Dr. James R. Lingley: This film gives an excellent view of the mass, which extends well out into the soft tissues, but there is no edema of the overlying soft tissues. The mass is smooth and sharply defined, with destruction of the anterior portion of the rib at the costochondral junction. There is also slight expansion and some new-bone formation.

Dr. Wallace: Would you say that the tumor probably had its origin in the rib or in the soft parts?

Dr. Lingley: I think that the expansion of the rib is in favor of the former location.

Dr. Wallace: There is nothing to suggest inflammation or osteomyelitis. Tuberculosis, of course, must be considered. The chest plate was negative, so that there was apparently no active pulmonary disease. The costochondral margin is a fairly frequent site for tuberculosis. I believe, however, that it is extremely unlikely in this case. Although the tumor did not have the appearance of a gumma, it certainly could have been, and I do not believe that we can definitely rule out such a diagnosis.

We therefore have the possibility of tumors, benign or malignant, that have their origin in bone. In considering the various cells from which such tumors arise, on the marrow side these cells may give rise to myeloma, which is usually multiple, of course, and with this duration extremely unlikely to be still localized. In addition, myeloma shows marked bone destruction, and one would not expect a sizable soft-part tumor. The reticuloendothelial cells presumably give rise to a Ewing tumor, which is also primarily a destructive lesion and could hardly cause a large, hard, soft-part tumor with so little destruction in the rib. The cartilage cells might result in either a chondroma or a chondrosarcoma. This lesion is at the costochondral junction, but it does not have the multilocular appearance or the marked expansion that is ordinarily seen with cartilaginous tumors. The osteoblasts, of course, give rise to osteoma, but in that situation one would not expect destruction. Could this have been osteogenic sarcoma? I think that it is extremely unlikely. The patient, who was over fifty years old, was not in the proper age group, and it is extremely rare to have osteogenic sarcoma in the rib — most of these tumors occur in the ends of the long bones. Could this have arisen from the osteoclastic cells, thus producing a giant-cell tumor? It had none of the characteristics of a giant-cell tumor on x-ray examination. Lymphoma must always be considered, and in the chest wall reticulum-cell sarcoma especially has to be thought of; I cannot rule it out. Many of the rarer tumors, such as the hemangioma, the eosinophilic granuloma and the plasma-cell tumor, should also be mentioned.

Could this have been a metastatic tumor? We have no lead for the site of the primary tumor, and

metastatic lesions are ordinarily punched out; such a large, soft-part tumor is unusual, although it is occasionally seen following carcinoma of the breast. If the breast had not been entirely normal, I think we might seriously consider that diagnosis. On the other hand, about once a year we see metastatic tumor from carcinoma of the breast in which the breasts are completely normal to palpation, and I recall one or two cases in which the pathologist had difficulty in finding the minute primary tumor that had given rise to widespread metastases.

The question then comes up whether this tumor originated outside the rib. This seems unlikely because of the x-ray findings.

I neglected to mention another definite possibility —a periosteal fibrosarcoma originating near the edge of the rib and involving it secondarily.

One other extremely rare tumor that is practically never seen is a myoblastoma. This ordinarily has its origin in the tongue in about half the reported cases, but it can occur anywhere in striated muscle. At Pondville Hospital we recently had 2 cases. One had its origin in the deltoid muscle, and the other in the muscles in the palm of the hand. In both cases the tumor was removed locally, and both patients died within eighteen months from widespread osseous metastases without local recurrence. The decision about the nature of the tumor is a matter of speculation, and it finally becomes necessary to do either a biopsy or an excision of the tumor before the real diagnosis becomes evident. But in this particular case I do not believe that tuberculosis or gumma can be ruled out. My first guess, and it is only a guess, is reticulum-cell sarcoma, and the second, fibrosarcoma, probably periosteal in origin.

Dr. Tracy B. Mallory: Dr. Lingley, would you care to make a diagnosis on the x-ray findings alone?

Dr. Lingley: As Dr. Wallace says, it is a guess, and we can tell definitely only on pathological examination. In this case the point of origin was somewhat in favor of a cartilaginous tumor. I would put chondrosarcoma as my first choice.

Clinical Diagnosis

Chondroma of rib.

Dr. Wallace's Diagnosis

Reticulum-cell sarcoma of rib.

Anatomical Diagnosis

Chondroma of eighth costal cartilage.

Pathological Discussion

Dr. Mallory: Dr. Herrera, will you describe the operative findings?

Dr. Rodolfo E. Herrera: We certainly did not believe that we could rule out a malignant lesion and for that reason decided on radical surgery, which was done at the first opportunity, with the danger of recurrence in mind. We knew that rib tumors have been known to spread through the marrow and to recur at different parts of the rib. Consequently, the chest was entered through the seventh intercostal space, and the tumor was explored from within the pleural cavity. It seemed to arise from the costochondral junction. The seventh and eighth interspaces were occupied by the tumor, and segments of the seventh and ninth ribs were removed by block excision and the eighth rib in toto, with part of the costal arch.

Dr. Mallory: The resected specimen showed a large cartilaginous tumor that evidently arose from the rib cartilage. As in most of these tumors, it looked essentially benign from the histologic point of view. We know, however, that these tumors must be treated with a good deal of caution. We have had one case, which Dr. Herrera mentioned, in which there was extension backward for a considerable distance through the rib. On the other hand, that was a single case. To my mind, the great danger in a case of this type is that certain cartilaginous tumors, in particular those in the rib and symphysis pubis, implant with the most extraordinary facility. It seems as if one tumor cell dropped in the wound almost inevitably grows and is followed by recurrence. We have had a number of such cases. In one, local resection was done, recurrence developed, the parietal pleura was removed, recurrence again developed on the visceral pleura, then some cells dropped down on the surface of the diaphragm, the diaphragm was resected and so on. In spite of the histologically benign appearance and the slight probability of metastases, these are cases that should be radically excised at the first operation, as was done in this case.

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The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

GREATER BOSTON COMMUNITY FUND

The Greater Boston Community Fund will conduct its campaign for funds to support its Red Feather Services during the first part of November. The Physicians' Division will solicit during the period October 28 to November 15, its quota being $23,000. The organization of the division is as follows: group chairman, Dr. John P. Monks; group vice-chairmen, Drs. Richard Stetson and George Sturgis; group committeemen, Drs. Archie Abrams, Myles Baker, Marshall Bartlett, Eugene Eppinger, Robert Joplin, Helen Pittman, Vernon Williams, Arthur Pier, Thomas Quigley, Gordon Donaldson, T. Cannon Eley, Paul Chandler, Charles Shedd, Walter Garrey and Benjamin Tenney. In addition, some ninety physicians will act as solicitors.

Everyone is well aware of the time and effort that many physicians are constantly giving without recompense to charitable institutions. On the other hand, contributions to the Fund represent their support as citizens of the hospitals and social agencies of this community. The drive is a vivid example of a democracy working at its best.

THE OUTLOOK FOR INFLUENZA

In a recent paper the Commission on Acute Respiratory Diseases[1] formulated a theory concerning the periodicity of influenza. It is based on published data concerning excess annual death rates from influenza and pneumonia since 1920 and on more precise information concerning the occurrence of epidemics of influenza A and B since 1932.

According to these workers, the sixteen widespread epidemics of influenza that occurred in the United States between 1920 and 1944 can be accounted for on the basis of two specific recurrent infections. Influenza A appears to have a cycle of two or three years, and influenza B a cycle of four to six years. They claim that no other influenza viruses have caused *widespread* epidemics in this country during the past twenty-five years. On the basis of this formulation, the probability of occurrence of future epidemics has been forecast within certain time limits, although exact predictions are not possible.

Specifically, the experience with the presumptive epidemics of influenza B is limited because the cycle is longer than that with influenza A and only a small number of past observations are reliable. The theory offered by the commission called for a widespread epidemic before the summer of 1946. At the time when the paper was written, there had been numerous small outbreaks of this infection that might have represented a return of influenza B five years after the previous epidemic, and there was insufficient evidence to indicate that this disease had caused an epidemic in a true sense. Only slight increases in the gross admission rates for respiratory diseases had occurred in the whole United States Army in the continental United States, although small outbreaks of influenza B occurred in certain

units. An influenza epidemic, however, occurred toward the end of 1945 that was roughly comparable in extent to the epidemic of influenza A that occurred in December, 1943.[2] For the country as a whole a rise in the occurrence of influenza began about the middle of November and reached a peak during the week ending December 22, with a definite falling off in the next two weeks. This epidemic, which involved nearly all geographic areas of the United States and also occurred in other countries, was definitely identified as being due to influenza B in all areas.

It was found that in the past twenty-seven years, seven of the eleven epidemics of presumptive influenza A occurred at an interval of two years and that the remaining four had a three-year interval. On the basis of that experience, there was more than an even chance that influenza A would reappear during the winter of 1945–1946. If influenza failed to occur in that season, the probability that it would appear in the following winter was even greater.

Influenza A was identified in isolated cases during and after the epidemic of influenza B that occurred last December. Small isolated outbreaks were recognized, but no definite epidemic of influenza A occurred. If the theory proposed by the commission is correct, the occurrence of an epidemic of influenza A during the coming fall and winter is almost a certainty. Since the recognized epidemics of influenza A and B in New England have occurred during December or January, an epidemic of influenza A may be expected during those months.

The etiology of the great pandemic of 1918 is not known. Predictions regarding the future occurrence of such a pandemic, if it was caused by an agent other than the virus of influenza A or B, cannot, therefore, be made at the present time.

Considerable information has been accumulated in recent years concerning preventive vaccines against influenza-virus infections, and the subject matter has been given considerable publicity both in the lay press and in the literature distributed by pharmaceutical firms. Physicians will have considerable difficulty in deciding whether or not such a vaccine should be given to any individual or group. In arriving at a decision, the known facts concerning the available vaccines, their efficacy and the untoward effects to be expected should be taken into consideration.

The influenza vaccines now available are prepared from fertile hens' eggs. After a stated period of incubation the eggs are inoculated with living influenza virus, which is then allowed to grow in the eggs — usually for two days. The allantoic fluid from these embryonated eggs is then harvested, and the virus contained in this fluid is concentrated by one of a number of methods and subsequently inactivated either by formalin or by other means, a preservative being added. The present vaccines usually contain about equal quantities of influenza A and B viruses, together with a certain amount of egg protein.

Influenza vaccines are now being marketed by several of the leading manufacturers of biologicals in this country. Their products are recommended for subcutaneous injection. The dose is a single injection of 1 cc. for adults, and two doses of 0.5 cc. each given a week apart are recommended for children. For batches of vaccine that produce excessive local or systemic reactions, the dose recommended for children should be used in adults as well.

The optimum protection to be expected from this vaccine, which is achieved about two weeks after the first injection, corresponds to the time of the maximum rise of antibody. Little if any protection may be expected within the first week after vaccination. The protection lasts at least three or four months and probably as long as a year or more. Its efficacy in protecting against both influenza A and B has already been fairly well established. The first opportunity to prove the effectiveness of these vaccines in the prevention of influenza B occurred last year. The reports indicate that influenza B was about ten times as frequent in unvaccinated persons as in those who were protected by the vaccine given in the manner suggested.[3] The results in influenza A as observed during the epidemic of 1943–1944 were not quite so good but point to a considerable degree of protection from the vaccine.[4] Generally speaking, the incidence of influenza in unvaccinated persons was two to six times, averaging about three times, as great as that in vaccinated

persons of comparable groups. The observations at that time were not all done under the most favorable conditions, and some were undertaken within too brief a period before the peak of the epidemic. Better results can probably be expected with the vaccines presently available if they are used under more favorable conditions and at a sufficient interval prior to the expected occurrence of an epidemic.

Reactions to the vaccine are of two types. One is related to sensitivity to egg protein and may be anything from mild urticaria to severe anaphylactic shock. The sensitization of persons so that they later develop allergic reactions from the injection of vaccine containing egg protein or from the ingestion of egg protein is a possibility, although sensitization of the latter type is probably rare. The second type of reaction is one related to the virus content of the vaccine. Symptoms simulating those of influenza may occur but are usually mild, of short duration and not incapacitating. They attest the efficacy of the virus and, when they occur, offer the best evidence that protection will be afforded. These reactions vary considerably with different batches of vaccine and are more frequent when the full dose is given in a single injection.

It should be borne in mind that the common cold and its complications are not prevented by the use of influenza vaccines, nor is protection afforded against bacterial infections such as streptococcal sore throat or against virus infections other than those caused by influenza.

In general, vaccination against influenza, if undertaken, should be done in the New England area during November or immediately on the first occurrence of typical cases of this disease. In the latter event, less protection may be afforded and those already exposed or who come in contact with the infection soon after inoculation may obtain no protection. Vaccination against influenza is not recommended in allergic persons unless there are special reasons for protecting them and unless it is known that they are not specifically sensitive to egg protein. Skin tests with diluted vaccine may be employed to test for such a sensitivity if vaccination is contemplated. Case histories should be obtained concerning sensitivity to egg protein and also concerning previous vaccination with materials that might contain egg protein. Vaccines against influenza, yellow fever and typhus fever were widely employed, particularly the last, among the armed forces that operated in North Africa and in the Mediterranean Theater, and all of them contained egg protein.

Vaccination is desirable in persons who have previously had severe experiences with influenza and its complications. It may also be recommended for those who are prone to recurrent attacks of upper or lower respiratory-tract infections that persist for a long time after attacks of influenza or the common cold. Large-scale immunization against influenza is recommended among groups in which it is important to minimize the occurrence of absenteeism during the period when epidemic influenza is likely to occur. In department stores, for example, the largest volume of business is transacted in the season when influenza epidemics usually occur. Certain industries that are geared to maximum production at these times might also be hard hit by an epidemic of influenza. In colleges and technical schools, particularly now that they have accelerated programs and much overcrowding, the occurrence of influenza might put the programs entirely out of gear. Under such conditions, large-scale vaccination may be highly desirable, but care should be taken to avoid the inclusion of persons in whom reactions might prove serious.

References

1. Commission on Acute Respiratory Disease. Periodicity of influenza. *Am. J. Hyg.* 43:29-37, 1946.
2. Prevalence of communicable diseases in the United States. December 2-29, 1945. *Pub. Health Rep.* 61:109-113, 1946.
3. Francis, T., Jr., Salk, J. E., and Brace, W. M. Protective effect of vaccination against epidemic influenza B. *J. A. M. A.* 131:275-278, 1946.
4. Commission on Influenza et al. Clinical evaluation of vaccination against influenza: preliminary report. *J. A. M. A.* 124:982-985, 1944.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Lowell	November 1	Albert H. Brewster
Salem	November 4	Paul W. Hugenberger
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Gardner (Worcester subclinic)	November 12	John W. O'Meara
Brockton	November 14	George W. Van Gorder
Worcester	November 15	John W. O'Meara
Pittsfield	November 18	Frank A. Slowick
Springfield	November 19	Garry deN. Hough
Fall River	November 25	David S. Grice
Hyannis	November 21	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

(*Notices on page xv*)

NOTICES

JOSEPH H. PRATT
DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Friday, November 1 — Some Newer Developments in Immunization. Dr. Geoffrey Edsall.
Wednesday, November 6 — Epidemic Hepatitis. Drs. H. E. MacMahon and Dr. Emmanuel Deutsch.
Friday, November 8 — The Surgical Relief of Severe Angina Pectoris: End results in eighty-three patients. Dr. James C. White.
Wednesday, November 13 — Pediatric Clinicopathological Conference. Drs. Charles H. Hollis and H. E. MacMahon.
Friday, November 15 — Carcinoma *in situ*. Dr. Tracy B. Mallory.
Wednesday, November 20 — Certain Peculiarities of Brain Metabolism. Dr. David Rapport.
Friday, November 22 — The Disordered Metabolisms in Thyrotoxicosis and Myxedema. Dr. J. D. Robertson.
Wednesday, November 27 — Immunity to Virus Infections. Dr. Charles A. Janeway.
Friday, November 29 — Newer Methods in the Study of Hemolytic Anemia. Dr. Jacob Neber.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

NEW ENGLAND HOSPITAL
FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, November 7, at 7:15 p.m., in the classroom of the Nurses' Residence. Dr. Felicia A. Banas will speak on the subject "Mesentery Thrombosis." Dr. Marion C. Sabia will be chairman.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 7

THURSDAY, NOVEMBER 7
7:15 p.m. Clinical Conference and Meeting of the Staff. Classroom, Nurses' Residence. New England Hospital for Women and Children.

FRIDAY, NOVEMBER 8
*9:00–10:00 a.m. The Surgical Relief of Severe Angina Pectoris: End results in eighty-three patients. Dr. James C. White. Joseph H. Pratt Diagnostic Hospital.
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

SATURDAY, NOVEMBER 9
7:00 p.m. Suffolk District Medical Society. Dinner Meeting. Harvard Club of Boston.

TUESDAY, NOVEMBER 12
12:00 m.–1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building, Boston City Hospital.
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*8:00 p.m. Harvard Medical Society. Amphitheater. Peter Bent Brigham Hospital.

WEDNESDAY, NOVEMBER 13
*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. Charles H. Hollis and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.
*10:30–11:30 a.m. Medical Clinic. Isolation Building Amphitheater. Children's Hospital.
*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.
*7:15 p.m. Graduate Seminar in Pediatrics. Children's Medical Service, Amphitheater 3A, Massachusetts General Hospital.

*Open to the medical profession.

OCTOBER 11–MAY 14. Metropolitan State Hospital. Page 398, issue of September 12.
OCTOBER 15–DECEMBER 5. Exhibition in Commemoration of Ether Centenary. Page 570, issue of October 10.
NOVEMBER 1–29. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Notice above.
NOVEMBER 5. Greater Boston Medical Society. Page 636, issue of October 24.
NOVEMBER 6. Cutter Lecture. Page 636, issue of October 24.
NOVEMBER 7. New England Hospital for Women and Children. Notice above.
NOVEMBER 9. Suffolk District Medical Society. Page 636, issue of October 24.

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